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STROKE PATIENTS IN THE INTENSIVE CARE UNIT.. IS THERE ANY BENEFIT?

ESSAY
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بسم الله الرحمن الرحيم

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ

خَلَقَ الْإِنْسَانَ مِنْ عَلَقٍ

اقْرَأْ وَرَبُّكَ الْأَكْرَمُ الَّذِي عَلَّمَ بِالْقَلَمِ

عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ

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Tarek Osman Raafat

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ABI	Atherothrombotic brain infarction
AF	Atrial fibrillation
AP	Angina pectoris
AVM	Arteriovenous malformation
BP	Blood pressure
CAA	Cerebral amyloid angiography
CBF	Cerebral blood flow
CE	Cerebral embolism
CHD	Coronary heart disease
CMRO2	Cerebral oxygen metabolism
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPP	Cerebral perfusion pressure
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerized tomography
CVR	Cerebrovascular resistance
CVS	Cerebral vasospasm
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
ECG	Echocardiography
GABA	Gama amino butyric acid
GCS	Glasgow coma score
HDL	High density lipoprotein cholesterol
ICH	Intracerebral hemorrhage

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ICP	Intracerebral pressure
ICU	Intensive care unit
LDL	Low density lipoprotein cholesterol
LPS	Lipopolysaccharide
MABP	Mean arterial blood pressure
MI	Myocardial infarction
MODS	Multiple organ dysfunction syndrome
MR	Magnetic resonance
NIDDM	Non insulin dependent diabetes mellitus
NPs	Natriuretic peptides
NPE	Neurogenic pulmonary edema
PAN	Poly-arteritis nodosa
PCD	Programmed cell death
PET	Positron emission tomography
PICH	Primary intracerebral hemorrhage
SAH	Subarachnoid hemorrhage
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SIRS	Systemic inflammatory response syndrome
SLE	Systemic lupus erythrematosus
SPECT	Single photon emission computed tomography
TCD	Transcranial Doppler
TIAs	Transient ischemic attacks
tAP	Tissue plasminogen activator
VLDL	Very low density lipoprotein

REVIEW OF LITERATURE

CHAPTER 1

INTRODUCTION

Stroke is the most common life threatening neurologic disease. It affects people in all ages and it is the third leading cause of death after heart disease and cancer *[Alfredsson et al., 1986]*.

In the elderly, the segment of the population where most stroke occurs, it was also a major source of disability leading to institutionalization *[Amery et al., 1985]*.

While medical and surgical therapies to reduce the damage from impending or recent-onset stroke must be pursued, it seems likely that the prevention will be the most effective strategy in reducing the ravages of cerebrovascular disease. Prevention will be facilitated by an understanding of predisposing host and environmental factors, which have been identified and determined in recent years. The relative impact of each of the risk factors becoming clearer and controlled clinical trials have demonstrated the efficacy of risk factor modification in stroke prevention *[Abbott et al., 1987]*.

Stroke is a clinical syndrome characterized by sudden onset of neurologic dysfunction of vascular etiology. There are two types of stroke: hemorrhagic and ischemic.

Frequency of stroke by types

The in-hospital assessment of stroke neurologist has helped document the stroke and determine stroke subtypes as well as to differentiate stroke from other neurologic diseases. Utilizing these data it was usually possible to determine if the stroke mechanism was hemorrhage or infarction and to distinguish subarachnoid from intraparenchymatous hemorrhage *[Wolf et al., 1992]*.

Ischemic strokes accounts for 65% of all stroke events and are attributed to cerebral arterial hypoperfusion from vessel narrowing, occlusion and systemic hypotension. Diagnosis of lacunar infarction was based on clinical and computerized tomography (CT) scan findings, while criteria for embolic infarction required a definite cardiac source for embolism. Distinguishing extracranial from intracranial cerebral infarction was made on clinical grounds, including non invasive carotid studies, angiography was performed by the study subjects'personal physicians rather infrequently *[Adams et al., 1986]*.

ABI, including infarction secondary to large vessel atherothrombosis as well as lacunar infarction, occurred most frequently in 44 percent of the total. Transient ischemic attacks (TIAs) alone accounted for approximately 21 percent of all stroke events and were more frequent in men, while cerebral embolism (CE), 21 percent overall, was marginally more frequent in women than men.

Hemorrhagic strokes is due to bleeding into brain tissue paranchyma or intracerebral hemorrhage (ICH) or bleeding into subarachinoid space (SAH). This stroke type is usually due to chronic hypertension, cerebral aneurysm, arteriovenous malformation, head injury or bleeding dyscraises. ICH accounted for 12 percent of all stroke events. SAH was more frequent in women than men and was also slightly more prevalent (6.6 percent) than ICH (5.1 percent).

CHAPTER 2

PATHOPHYSIOLOGY

Risk factors for stroke

Identification of risk factors for stroke, awareness of its relative importance and of its interaction with other precursors, may yield important clues concerning pathogenesis and thereby lead to stroke prevention *[Abbott et al., 1986]*.

Risk factors for stroke from atherosclerosis of the carotid and vertebral arteries may differ in their impact when compared to stroke resulting from lacunar infarction. Nevertheless, certain predisposing factors, particularly elevated blood pressure (BP) seem common to most stroke types *[Bonita, 1989]*.

Race

Blacks had higher hospitalization rates, a higher prevalence of hypertension and diabetes, and more ICH and less extracranial and large artery atherosclerotic disease than whites *[Wolf et al., 1992]*.

Compared with whites, blacks have higher death rates from stroke *[Gillum, 1988]*.

Physical activity

Work-associated vigorous physical activity has been linked to lower coronary heart disease (CHD) incidence and of myocardial infarction (MI) but had no reduction in

stroke incidence *[Leon et al., 1987]*. Vigorous exercise may exert a beneficial influence on risk factors for atherosclerotic disease by reducing elevated BP as a result of weight loss and by reducing the pulse rate, raising the high density lipoprotein cholesterol (HDL) and lowering the low density lipoprotein cholesterol (LDL), improving glucose tolerance and by promoting a lifestyle conductive to favorably changing detrimental health habits such as cigarette smoking *[Wolf et al., 1992]*.

Anger expression and incident stroke

Men who frequently expressed anger outwardly were twice as likely to experience a stroke in the subsequent 8 years than men who were more even-tempered, after taking into account known stroke risk factors in multivariate analysis *[Everson et al., 1999]*. Other styles of anger expression, namely anger-in and anger-control, were not associated with increased stroke risk *[Everson et al., 1997]*.

The lack of association between anger in and stroke risk is somewhat surprising for 2 reasons first, much of the literature focused on the role of anger and hostility in cardiovascular mortality and morbidity, and particularly hypertension, has focused on the association between inhibition or suppression of anger and cardiovascular end points *[Kawashi et al., 1996]*. Second Everson et al. in (1999), reported that both anger-out and anger-in, in the extreme, are associated with excess risk of hypertension after 4 years. They also noted that expressions of hostility or anger that are deviations from normal in either direction may be related to adverse cardiovascular consequences. It

is unclear why anger-in would be related to hypertension risk but not stroke risk. They found an association between anger-out and risk of stroke. Results were stronger for ischemic strokes than for all strokes combined, and the effect of anger on stroke risk was pronounced among men with a history of ischemic heart disease and essentially nonexistent among those without *[Sacco et al., 1997]*. It is possible that anger could increase the likelihood of a stroke triggered by vasoconstriction or blockage of a blood vessel to the brain, which would be more likely to occur in persons with prevalent ischemic heart disease than without *[Everson et al., 1999]*.

Prior research has shown that anger and hostility are associated with excessive autonomic and neuroendocrine activation *[Laude et al., 1997]*.

In addition, recent studies indicate that anger and hostility are associated with increased platelet activation and reactivity *[Markovitz, 1998]*.

Hypertension

Hypertension is the most powerful risk factor of stroke, and higher levels of systolic and diastolic BP (average approximately 190mmHg and 100mmHg respectively) have been associated with an increased incidence of ischemic and hemorrhagic stroke in people of all ages and both sexes *[Kannel, 1996]*. Diastolic BP has been thought to be of greater importance than systolic pressure *[Rutan et al., 1989]*.

The cause of acute hypertensive response is unknown, but major contributors may be the Cushing response or catecholamine discharge *[Adams and Powers, 1997]*. Vascular damage in the form of lipohyalinosis and microaneurysm formation occurs in the brains of patients with chronic hypertension *[Menotti et al., 1996]*.

It has been demonstrated that antihypertensive therapy effectively reduces morbidity and mortality of stroke in hypertensive subjects, including elderly patients with isolated systolic hypertension *[Makino et al., 2000]*.

It is demonstrated that untreated hypertensives who needed treatment according to the severity of their hypertension and the presence of additional cardiovascular risk factors had an increased risk of stroke compared with pharmacologically treated hypertensives whose blood pressure level was controlled *[Klungel et al., 1999]*.

Therefore, there is no doubt that control of hypertension is particularly important for the prevention of stroke. Du et al. in 1997, suggested that control of BP to less than 150/90mmHg is required for optimal stroke prevention. In the hypertension optimal treatment (HOT) study, the lowest incidence of stroke occurred at a mean achieved systolic BP of 142 mmHg, while the lowest diastolic BP did not predict the onset of stroke *[Hansson et al., 1998]*.

However, there is persistent excess cardiovascular morbidity in treated hypertensive patients *[Verdecchia et al., 1994]*. The level of BP before the onset of stroke is less well characterized and the risk of stroke

in treated patients has not been clarified well. A number of treated patients still have high BP and often have other cardiovascular risk factors and complications *[Muratani et al., 1996]*.

The incomplete control of hypertension may be related to the risk of stroke *[Du et al., 1997]*. On the other hand, an excessive decrease in BP may increase cardiovascular complications. Minami et al. in 1998, observed that low diastolic BP is associated with increased recurrence of stroke or MI. It has also been suggested that the level of optimal BP may be age dependent *[Curb et al., 1996]*.

Makino et al. in 2000, found that mean BP for the 12 months before the onset of stroke in treated hypertensive patients was not significantly different from that in treated hypertensive patients without stroke. In subjects aged less than 70 years, however, the mean systolic BP was significantly higher in patients with than in those without stroke. Also, they suggested that higher BP (particularly for patients aged less than 70 years) and the presence of cardiovascular risk factors other than hypertension and target organ damage increase the risk of first stroke in treated hypertensive patients.

The relative risk of stroke in hypertensive subjects decreases with age, although the absolute risk for stroke is high in elderly hypertensive subjects *[Omae and Ueda, 1988]*. In another study, the relative risk for stroke mortality was 10-fold higher in hypertensive subjects aged less than 60 years than normotensive subjects of similar

age, but it was 3-fold higher in hypertensive subjects aged more than 60 years *[Ueda et al., 1988]*.

In study done by Makino et al. in 2000 regarding to stroke subtype, patients with brain hemorrhage had higher diastolic BP before the onset of stroke than those with other subtypes. This is, in part, due to alteration in intracranial hemodynamics and intracranial pressure-volume dynamics. Mean systolic BP was relatively high in patients with lacunar brain infarction, and this group had significantly higher systolic BP than the control group. so brain hemorrhage and lacunar infarction are more closely related to hypertension than other subtypes.

In the elderly, isolated elevation of systolic pressure becomes highly prevalent. Stroke and cardiovascular disease incidence was significantly increased in persons with isolated systolic hypertension *[Colandrea et al., 1970]*.

Risk was proportionately related to the level of systolic pressure even after diastolic pressure, age and digital pulse wave configuration (an index of arterial rigidity) were taken into account *[Grove et al., 1997]*.

In addition, it is clear that incidence of stroke generally and ABI specifically, is related to level of systolic pressure among persons with diastolic BP below 95mmHg *[Davis et al., 1998]*.

An understanding of cerebrovascular physiology, intracranial pressure (ICP) dynamics, and the relationship

between the two is essential to understand the central issues surrounding blood pressure management in patients with acute ICH. The primary function of the cerebral circulation is to provide adequate glucose and oxygen to the brain parenchyma. Tight coupling exsits between cerebral blood flow (CBF) and cerebral metabolism and is referred t as metabolic autoregulation *[Lassen and Christensen, 1976]*. The mean adult CBF is $50ml\text{-}100g^{-1}.\ min.^{-1}$

CBF is determined by its driving pressure, cerebral perfusion pressure (CPP) and the resistance to this pressure by the following relationship: CBF=CPP/CVR where CVR is cerebrovascular resistance. CPP is the difference between mean arterial blood pressure (MABP) and mean cerebral venous pressure. Cerebral venous pressure is usually negligible except in the presence of intracranial hypertension, in which case it is essentially equal to ICP. Thus, the relationship CPP=MABP-ICP is more practically applicable *[Adams and Powers, 1997]*.

Changes in CVR is mediated by dilation or constrictioin of cerebral resistance vessels (pial arterioles) *[Fog, 1939]*. The ability to maintain constant CBF as CPP varies is referred to as pressure autoregulation *[Strandgaard and Paulson, 1992]*. In normotensive people, this range is usually assumed to be 60 to 150mmHg of CPP. However, the lower limit of autoregulation is higher, occuring at 85$\pm$5mmHg of CPP. Outside this range, CBF

is pressure passive changing in proportion to the change in CPP *[Powers, 1993]*.

Autoregulation become impaired after a number of cerebral insults. In tissue subjected to progressively severe ischaemia, autoregulation becomes increasingly pressure passive with progressively lower CBF at all levels of CPP compared with normals *[Dirnayl and Pulsinelli, 1990]*. Autoregulation also has been shown to be deranged in several other types of acute brain injury including SAH, traumatic brain injury and may be deranged in ICH *[Adams and Powers, 1997]*.

When CPP falls below the lower limit of autoregulation, decreases in CVR are inadequate to maintain normal CBF. Initially, as CBF falls, cerebral oxygen metabolism ($CMRO_2$) is maintained. Normally, the brain extracts one third of the oxygen delivered by blood. As CBF decreases, this oxygen extraction increases, sometimes to a high percentage of that delivered, to maintain normal $CMRO_2$ *[Adams and Powers, 1997]*. This compensation is effective to a degree, but after oxygen extraction is maximized, $CMRO_2$ decreases and ischaemia (CBF that is inadequate to meet metabolic needs) occurs.

Astrup et al. in 1981 coined the term "ischemic penumbra" to describe cerebral tissue with CBF values between an upper limit corresponding to electrophysiologic dysfunction and a lower limit corresponding to disruption

of cellular homeostatic function with membrane dysfunction and ultimately cell death.

At CPP above the range of autoregulation, CBF increases with CPP. In animal studies, the progressive arteriolar, vasoconstriction that occurs with increasing CPP in the autoregulatory range is replaced at higher CPP by progressive diffuse dilation of pial arterioles with areas of segmental aneurysmal outpouching *[Konros et al., 1981]*. If CPP exceeds the autoregulatory range for even brief periods of time, normal vascular reactivity is impaired (vasoparalysis) for hours upon return to habitual CPP levels *[Adams and Powers, 1997]*.

With chronic hypertension, there is compensatory shifting of the autoregulatory curve so that autoregulation continues over a similar range, but at higher pressures *[Strandgaard and Paulson, 1992]*. In individuals with severe and chronic hypertension, the lower limit of autoregulation is set at a higher CPP, which may be close to habitual CPP for normotensive individuals. This makes the risk of cerebral ischaemia greater in these patients if their BP is inappropriately normalized. The shifting of the upper limit of autoregulation, on the other hand, does afford some protection against vessel disruption and vasoparalysis with higher CPP. Usual CPP in some persons with hypertension may run at high levels above the upper limit of autoregulation for normotensive individuals without producing any acute problems *[Adams and Powers, 1997]*.

Stroke and coronary heart disease incidence according to severity of hypertension

For mild or borderline elevation of BP, CHD is the chief cardiovascular outcome while at higher levels of pressure, stroke is more likely *[Wolf et al., 1992]*. Stroke was also more likely to be the initial manifestation of cardiovascular disease among those with definite hypertension, compared with normotensives *[Mooe et al., 1997]*.

Several cardiac disorders, e.g. atrial fibrillation (AF), mitral valve disease, acute MI, angina pectoris (AP) and non Q-wave infarction, are associated with an increased risk of ischemic stroke *[Hart, 1992]*.

Among transmural MIs, anterior wall infarcts are more likely to lead to stroke than transmural infarcts at other sites *[Wolf et al., 1992]*.

A hemorrhagic stroke during the first 24 hours is a well-known consequence of thrombolytic therapy *[Gore et al., 1995]*.

In 1999, Mooe et al., provided important information about the time relationship between MI and first-ever stroke. It was obvious that most strokes occur within the first few days after a MI, and the mortality is high if a MI is complicated by a stroke. Death from progressive stroke, possibly reflecting the more extensive cerebral damage after MI *[Loh et al., 1997]*.

The pathophysiology of stroke after MI is unclear. One hypothesis is that embolism from a left ventricular

thrombus is a common mechanism *[Vaitkus and Barnathan, 1993]*. However, this has been disputed, and left ventricular thromboembolism can explain only a small fraction of MI related strokes *[Bodenheimer et al., 1994]*. Other important mechanisms, which were suggested in the 1940s, may be in situ thrombosis and artery-to-artery embolism because of atherosclerosis and unfavorable hemodynamics *[Mooe et al., 1999]*. Moreover, an acute MI is followed by increased fibrinogen levels and a pronounced sympathetic activation which may facilitate thrombus formation in patients with atherosclerosis in the aorta and the cervical and cerebral arteries *[Tanne et al., 1993]*. Hypothetically, the prothrombolic mechanisms following a MI may result in more dynamic and extensive thrombus formation, which at least in part may explain the occurrence of the neurological features.

AF was acknowledged as a predisposing factor to stroke. Chronic AF without valvular heart disease, previously considered to be innocent, but recently it had been associated with increased incidence of stroke *[Wolf et al.,. 1991]*. AF is also the most prevalent cardiac arrhythmia in the elderly *[Wolf et al., 1987]*. Although, the prevalence of other cardiac contributors to stroke also increased with age, the increased incidence of stroke in persons with AF was probably a consequence of the AF and not the associated CHD or cardiac failure *[Wolf et al., 1992]*. In patients with ischemic stroke Wong's data in 1999 showed that AF and ischemic heart disease are independent risk factors for early death.

Blood lipids

Total serum cholesterol is significantly and independently related to the development of CHD *[Wolf et al., 1992]*. HDL has an inverse association and LDL a direct relationship to incidence of CHD *[Yano et al., 1989]*. Also, Makino et al. in 2000 found that the level of HDL cholesterol tend to be lower in the stroke group.

A surprisingly consistent finding has been the relationship between low serum cholesterol and increased incidence of ICH. The interaction of high diastolic BP and low serum cholesterol in promoting ICH suggeted to some investigators "that very low serum cholesterol levels weaken the endothelium of intracerebral arteries, resulting in hemorrhagic stroke in the presence of hypertension" *[Iso et al., 1989]*. These data also provide evidence for a direct relationship between high levels of total serum cholesterol and ischemic stroke, particularly in hypertensives. Generally, the relationship to stroke may be obscured by the differing influence of lipids on the varying vascular pathologies underlying stroke *[wolf et al., 1992]*. Low levels of serum cholesterol, less than 180mg/dl, and particularly less than 160mg/dl, seem to promote ICH and perhaps SAH while elevated levels foster large vessel atherothrombosis *[Hill et al., 2000]*.

Obesity

Obese persons have higher levels of BP, blood glucose, and atherogenic serum lipids, and on that account alone could be expected to increase stroke incidence *[Wolf et al., 1992]*. In 1990, Folsom et al., found that the pattern of obesity is also important, central obesity and abdominal deposition of fat were more strongly associated with atherosclerotic disease.

Diabetes

It is well recognized that established diabetes mellitus (DM) is an important risk factor for the development of stroke *[Wannamethee et al., 1999]*. However, at all ages both men and women with glucose intolerance have approximately double the risk of ABI as non diabetics *[Wolf et al., 1992]*. The development of type 2 diabetes is preceded by a prolonged period of insulin resistance with compensatory hyperinsulinemia and a gradual onset of hyperglycemia. Hyperglycemia and hyperinsulinemia are both integral to the pathogenesis of type 2 diabetes, and both have been associated with increased risk of CHD *[Tuomilehto et al., 1996]*. The role of hyperglycemia and hyperinsulinemia as risk factors for stroke is even less certain *[Perry et al., 1996]*.

It has been demonstrated that the relationship between glucose intolerance or hyperglycemia and risk of stroke in nondiabetics have yield inconsistent results *[Qureshi et al., 1998]*. A positive but non significant relationship was seen between hyperglycemia and total stroke after adjustment

for cardiovascular risk factors *[Wannamethee et al., 1999]*. Those apparently non diabetic at screening who manifested diabetes during the average 17-year follow-up were at increased risk of a magnitude similar to those with diabetes at screening *[Tuomilehto et al., 1996]*.

It had been shown that proteinuria was an independent risk factor for stroke in patients with non insulin dependent diabetes milletus (NIDDM). This support the hypothesis that proteinuria reflects a more generalized vascular process, in agreement with a previous report by Miettinen et al. in 1996 which, based on a 7-year follow-up, showed that proteinuria is a predictor for stroke in nondiabetic and diabetic subjects.

Proteinuria seems to be an underlying disorder itself, predicting all causes and cardiovascular mortality *[Eastman and Keen, 1997]*. The mechanisms of the association between proteinuria and cardiovascular disease are poorly understood. It has been proposed that albuminuria is associated with the increase in both albumin and fibrinogen transcapillary escape role, which reflects widespread vascular damage or endothelial dysfunction *[Deckert et al., 1989]*. Furthermore, albuminuria has been shown to be related to an increased extravascular coagulation, which leads to an increased release of von willebrand factor, contributing to the formation of microthrombi and platelet plugs, followed by areas of non-perfusion *[Knobl et al., 1993]*. These support the hypotheses that increased urinary protein or albumin excretion is associated with increased mortality and

widespread vascular injury, which contribute to the risk of stroke *[Miettinen et al., 1996]*.

Hyperglycemia is related to atherogenic lipoprotein changes and is also a procoagulant state. Hyperglycemia can decrease prostacyclin synthesis, increase thrombosis formation, and cause glycosylation of proteins in the artery wall *[Lehto et al., 1996]*. These conditions, which are related to poor metabolic control, can cause atherosclerosis, which could contribute to increase the risk of stroke.

The detrimental effects of diabetes on the outcome of cerebrovascular disease can explain why diabetics have poorer outcome after stroke and coronary artery disease than non diabetics *[Haffiner et al., 1998]*.

Hematocrit

A relationship between high-normal hematocrit level and incidence of cerebral infarction was demonstrated. Increased concentration of red cells in combination with high blood fibrinogen levels raises blood viscosity *[Wolf et al., 1992]*. Reduction of high-normal hematocrit by venesection has decreased blood viscosity and correspondingly increased CBF *[Reed, 1990]*.

Fibrinogen

Serum fibrinogen has been implicated in atherogenesis and in arterial thrombus formation. Fibrinogen has A substantial and significant independent impact on cardiovascular disease incidence, including stroke *[Wilhelmson et al., 1984]*. In a study done by Kannel et al.

in. 1987, fibrinogen in combination with elevated systolic BP, was found to be a potent risk factor for stroke. Fibrinogen was also positively associated with most of the major risk factors for stroke, including age, hypertensive status, hematocrit level obesity and diabetes.

Leptin

Leptin is a hormone secreted from adipose tissue, its level is proportional to the adipose tissue mass in the whole body. It acts centrally on the hypothalamus by decreasing food intake and increase energy expenditure. In obesity its level is high but there is resistance to its action. Up till now, it has no normal level, however, its value is considered normal if body mass index is less than 25kg/m^2 *[Bray and York, 1997]*.

In 1999 Soderberg and his colleagues found that circulating levels of leptin were found to be significantly associated with other risk markers, including elevated BP, body mass index, glucose, insulin, and cholesterol levels. In multivariate analysis, high leptin retained its position as a powerful marker for the future risk of hemorrhagic stroke *[Haffiner et al., 1997]*. In fact, leptin (together with high BP) emerged as the strongest independent risk marker for hemorrhagic stroke *[Soderberg et al., 1998]*. In contrast, hypertension was the only remaining risk factor for ischemic stroke in a multivariate model after adjustment for covariates, including leptin and other unknown risk markers for ischemic stroke *[Soderberg et al., 1999]*. Also, they have shown that a high leptin level is

a strong risk marker for first-ever acute MI in men independent of other known acute MI risk factors.

In evolutionary terms, the role of leptin has been suggested to be that of a protector against the effects of starvation *[Schwartz and Seeley, 1997]*. However, hyperleptinemia may contribute to the development of cardiovascular disease via its effects on BP regulation, insulin sensitivity, and a number of other hormonal interactions *[Bray and York, 1997]*.

In 1999 Soderberg et al's data supported a close relationship between leptin and BP, as the combination of high levels of leptin and high diastolic or systolic BP was a strong predictor for hemorrhagic stroke. In contrast, the combination of high levels of leptin and BP did not predict ischemic stroke *[Haynes et al., 1997]*.

Soderberg et al. in 1999, found a close association between circulating leptin and insulin levels. Impaired insulin sensitivity has been associated with cardiovascular disease *[Haffiner et al., 1997]*. Insulin resistance has been shown to be associated with atherothrombotic stroke (but not with lacunar or cardioembolic strokes) in nonobese men and women *[Shinozaki et al., 1996]*.

The association between cholesterol levels and stroke risk is not clear cut *[Sharrett et al., 1994]*. Interestingly, low HDL-cholesterol levels, which correlate with extracranial carotid atherosclerosis and are a key feature of the dyslipidemia associated with insulin resistance and central obesity, are associated with high leptin levels *[Heiss et al., 1991]*.

Central obesity may be of importance in determining leptin levels in men and indirect measures of central obesity, such as visceral fat area or waist circumference, are associated with increased leptin levels in men and postmenopausal women *[Haffiner et al., 1996]*.

This is of interest, because central obesity, rather than the obesity involving hip and thighs, relates to an increased stroke risk *[Ronnemaa et al., 1997]*.

A final mechanism behind increased leptin, the insulin resistance syndrome, and cardiovascular disease (including stroke) may be dysfibrinolysis *[Juhan-Vague and Alessi, 1996]*. It has been shown that elevated leptin levels are associated with low levels of tissue plasminogen activator (tPA) activity and high levels of plasminogen activator inhibitor-1 *[Sacco et al., 1997]*.

Homosystein

Kristensen et al. in 1999 suggested that an exaggerated total homocystein increase after methionine loading represents a cerebrovascular risk factor in ischemic stroke. This association was present also after adjustment for other conventional cerebrovascualr risk factors, including fibrinogen. Also, they suggested that homocysteinemia after methionine loading is associated with a hypofibrinolytic state.

Homocysteine may thus participate as an additional 'hit' in abnormalities in coagulation and vascular cell functions in young adults with ischemic stroke *[Refsum et al., 1998]*.

Calcium, potassium and Magnesium intake and risk of stroke

In 1996 Abbott and his colleagues showed an inverse relation between calcium intake and risk of ishemic stroke, an association restricted to dairy calcium intake and specifically to milk consumption. Iso et al. in 1999b observed that the inverse association with dairy calcium intake was not restricted to milk but was also observed for yogurt, hard cheese and ice cream. Also, they suggested an inverse association between non dairy calcium intake and risk of ischemic stroke, although the relation was not as strong as for dairy calcium. These results suggest that calcium intake per se may reduce risk of ischemic stroke.

The mechanisms by which calcium intake could reduce risk of ischemic stroke are not well elucidated. A meta-analysis of randomized clinical trials concluded that calcium supplementation may slightly reduce systolic BP, by 0.9 to 1.3mmHg, but not diastolic BP *[Allender et al., 1996]*. In addition to a hypotensive effect, increased calcium intake reduced platelet aggregation, providing another mechanism that may lead to reduction of risk of ischemic stroke *[Iso et al., 1999b]*. In hypercholesterolemic persons, calcium supplementation has reduced serum total cholesterol, which may also contribute to reduce the risk of ischemic stroke *[Hebert et al., 1997]*.

Dietary potassium intake also was associated with reduced risk of ischemic stroke, but the relation was far from statistically significant after simultaneous adjustment for calcium intake *[Iso et al., 1999b]*. They also found no

association between potassium supplement use and risk of ischemic stroke. A meta-analysis of randomized clinical trials found that potassium supplementation reduces both systolic (-5.9mmHg) and diastolic BP (-3.4mmHg) *[Cappuccio and MacGregor 1991]*. Hypertensive rats given a high-potassium diet had decreased vascular smooth muscle cell proliferation that may contribute to a reduced risk of stroke *[Tobian 1986]*. In a study done by Lee et al. in 1988 an inverse association between potassium intake and risk of fatal ischemic stroke has been showed, but not of nonfatal ischemic stroke. In a study done by Ascherio and his coworkers in 1998 indicated an inverse assocation between potassium intake and risk of all stroke and ischemic stroke, particularly among hypertensive men. They also found no independent association between magnesium intake and risk of stroke. But a weak inverse trend was found in the age and smoking-adjusted analysis *[Witteman et al., 1989]*.

Alcohol consumption

In subjects with a high-risk source of cardiogenic brain embolism, hypertension was the most significant risk factor for stroke, but recent heavy alcohol intake was another important and independent risk factor *[Wannamethee and Shaper, 1998]*. Hillbom et al. in 1999, found that recent heavy drinking of alcohol increased the risk of cardioembolic stroke, whereas former heavy drinking and recent light drinking did not. There are several possible mechanisms that could explain the effect. First, heavy drinking of alcohol precipitates cardiac arrhythmias *[Shanmugan and Regan, 1996]*. The

propagation of thrombi is certainly enhanced by cardiac arrhythmias, and alcohol, even in modest doses, has the potential to produce arrythmias in patients with a history of chronic alcohol consumption and heart disease *[Hart 1992]*. It is also conceivable that some subjects may show genetically greater sensitivity to the arrhythmogenic effects of alcohol than other *[Hillbom et al., 1999]*. Second, alcohol and possibly also acetaldhyde seem to be cardiotoxic agents that cause alcoholic cardiomyopathy. There are case reports which demonstrate that alcoholic cardiomyopathy results in cardiogenic brain embolism *[Gonzalez et al., 1988]*.

Hillbom and his colleagues in 1999 observed that heavy alcohol intake within 24 hours before the onset of stroke was a risk factor for stroke due to large-artery atherosclerosis, this was explained by the effect of acute severe alcoholic intoxication on circulation. A local thrombus attached to the arterial wall may be easily dislodged by a sudden marked increase of blood flow, which frequently follows the acute intake of an intoxicating dose of alcohol *[Sacco et al., 1999]*. Acute alcohol intoxication has been named as a precipitating factor in stroke in young people, both in thrombotic stroke and in SAH. Increases in alcohol consumption were related to increasing levels of BP, cigarette smoking and to lower serum cholesterol levels, all risk factors for ICH *[Wolf et al., 1992]*.

Cigarette smoking

Cigarette smoking, a powerful risk factor for MI and sudden death has been clearly linked to brain infarction, as well as to ICH and SAH *[Colditz et al., 1988]*. There is an increased risk of SAH as well as thrombotic stroke in cigarette smokers *[Wolf et al., 1992]*. Relative risk of SAH showed a dose-response relationship from a 4-fold in light smokers to 9.8-fold in smokers of 25 or more cigarettes daily *[Colditz et al., 1988]*.

The association between cigarette smoking and SAH from aneurysm was also found in men (as well as in women) *[Bonita, 1989]*. Wolf et al. in 1992, suggested that smoking promoted a temporary increase in BP, which, acting in concert with the "metastatic emphysema effect", was responsible for SAH from cerebral aneurysm.

Acetylsalyclic acid use and risk of stroke

One important finding of Wong's study in 1999 was the observation that prior use of antiplatelet drugs, mainly acetylsalyclic acid, nearly halved the risk of early death among patients with ischemic stroke. The benefit of antiplatelet drugs in the secondary prevention of stroke and cardiovascular diseases is now firmly established *[Hennekens et al., 1997]*. However, ischemic stroke may still occur in patients taking regular antiplatelet drugs. In this group of patients, it remains uncertain whether prophylactic use of acetyl salyclic acid reduces the severity of subsequent stroke. In other clinical situations in which acute arterial occlusion occurs, acetyl salyclic acid has been shown to abate the clinical manifestation *[Garcia-*

Dorado et al., 1995]. In 1999a, Iso et al., found differential effects of acetylsalycilic acid use by stroke subtypes, acetylsalyclic acid was associated with a reduced risk of large-artery occlusive infarction and an increased risk of SAH. Acetylsalycilic acid irreversibly inhibits synthesis of thromboxane A2 in platelets and cyclooxygenese-dependent aggregation of platelets *[Miller et al., 1993].*

On the other hand, a single dose of acetyl salyclic acid substantially reduces synthesis of the strong vasodilator, prostacyclin (PGI2) in vascular endothelial cells *[Iso et al., 1999a].* An excess risk of SAH with high dose of acetylsalicylic acid is possibly due to the combined inhibitory effects of synthesis of thromboxan A2 in platelets and prostacyclin in vascular endothelial cells *[Grilli et al., 1996].*

In cerebrovascular disease, Riepe and his colleagues in 1997, showed that patients who had a stroke while taking acetyl salyclic acid tend to have a less severe stroke.

Anticoagulation for primary stroke prevention

One of the most important recent advances in primary stroke prevention is the demonstration that warfarin can substantially reduce the risk of stroke in patients with AF *[Feinberg 1998].* However, not all patients with AF will benefit equally by long-term anticoagulation, and the greatest benefit will be seen in those with the greatest risk of stroke *[Kalra et al., 1999].* They also suggested that, treatment decisions to anticoagulate can be made safely, without recourse to echocardiography (ECG), in all patients who have clinical

risk factors and no contraindications to anticoagulation, regardless of the age of patient.

Oral contraceptives

An increased risk of stroke was reported in users of oral contraceptives, particularly in older women, that is, above age of 35 years, and predominantly in those with other cardiovascular risk factors, particularly hypertension and cigarette smoking *[wolf et al., 1992]*. Surprisingly, the association between cigarette smoking, oral contraceptives, and stroke was primarily related to SAH *[White, 1991]*. However, the mechanism of stroke in oral contraceptive users is unclear. Cerebral infarction is more likely to be due to thrombotic disease than to atherosclerosis, it is known that clotting is enhanced by oral contraceptive-induced increased platelet aggregability and by its alteration of clotting factors to favor thrombogenesis *[Wolf et al., 1992]*.

Pathology of stroke

The development of a focal neurologic deficit is designated stroke if the cause of the deficit is thought to be the consequence of a local disturbance in the cerebral circulation *[Keller et al., 2000]*. The main causes of these, frequently abrupt, changes in brain circulation are a reflection of either obstruction of the CBF or rupture of the wall of a vessel supplying the brain or spinal cord *[DeGraba et al., 1992]*.

Vascular disease: (angiopathies)

Atherosclerosis is a source of brain infarcts, particularly in the territory of the basilar and internal carotid arteries *[Yue et al., 1997]*. Stroke due to atherosclerosis or so-called ABI remain numerically the most common neurologic disorder among adults *[Yatsu and Fisher 1989]*.

Expanding knowledge about the pathogenesis of atherosclerotic plaque development and the cellular contributors to the process are important from a pathophysiologic and potentially therapeutic perspective *[DeGraba et al., 1992]*. The earliest lesion of atherosclerosis is the fatty streak which can be seen as early as late childhood or early adolescence *[Stary 1987]*. Fatty streaks are grossly visible as areas of yellowish discoloration of the intimal surface of large to medium-sized arteries, when fat staining techniques are employed *[Cashin-Hemphill et al., 1990]*. On a microscopic level, fatty streaks are noted to consist primarily of lipid-laden macrophages known as foam cells *[Mitchinson and Ball, 1987]*.

The macrophages gain entry into the arterial wall at very early stages in the atherogenic process *[Masuda and Ross, 1990]*. T-lymphocytes are also present in early plaques *[DeGraba et al., 1992]*.

Fatty streaks progress, typically over many years, fibrous plaques begin to develop in middle-aged and older adults *[McGill, 1988]*. These fibrous plaques develop are

more localized than fatty streaks, occurring at arterial branch points or opposite arterial bifurcation.

Small arterioles are commonly observed at the periphery of the plaque and engender the possibility of hemorrhagic transformation in some fibrous plaques *[DeGraba et al., 1992]*. The complicated plaques represents the most advanced stage of atherogenesis, and these plaques are similar to fibrous plaques. However, they commonly contain hemosiderin, areas of intraplaque calcification, and disruption of the endothelial lining *[McGill, 1988]*.

Plaques usually enlarge insidiously over decades. It is only when the plaque burden reaches a substantial percentage of the arterial luminal diameter that symptoms typically occur *[Bassiouny et al., 1989]*. Plaque destabilization leading to symptom development is an important consideration concerning potential prevention of atherosclerotic complications, such as ischemic stroke or MI.

Cellular contributors

The major cellular contributors to large vessel atherosclerosis appear to be monocytes/macrophages, smooth muscle cells, and endothelial cells *[DeGraba et al., 1992]*. Ross in 1988 suggested that, the earliest initiating event for atherogenesis is functional or morphologic injury to the endothelial lining of large to medium-sized arteries. Endothelial injury can be mediated by a number

of processes, including hypertension, hyperlipidemia, cigarette smoking and radiation *[DeGraba et al., 1992]*. This leads to the early adhesion and then intimal migration of circulating blood monocytes into the vessel wall *[Ross, 1988]*. Lipids enter the vessel wall via the endothelial cells in a complex fashion involving both active and passive transport *[Jaffee, 1987]*. Vessel wall monocyte-derived macrophages imbibe LDL cholesterol to form foam cells, a hall mark of early plaque development *[DeGraba et al., 1992]*.

Cytokines, released by macrophages, smooth muscle cells and perhaps, T-lymphocytes, which also present in early atherosclerotic plaque, may play a role in cellular interactions as well *[Buchwald et al., 1990]*. Synthesis of the connective tissue elements by smooth muscle cells lead to further plaque development and matrix formation *[Nathan, 1987]*. Cell necrosis and death of lipid-laden cells generates the lipid core associated with more advanced lesions *[Sempos et al., 1990]*. As this dynamic and complex process proceeds over decades, the plaque slowly enlarges, leading to luminal compromise and ultimately symptom development *[DeGraba et al., 1992]*.

Low-density lipoprotein oxidation and cellular aspects of atherogenesis

It is clear that lipids play an important role in atherosclerotic plaque development, as do the cellular conributors. Linking the interaction between the cellular contributors to the lipid aspects is an important aspect of atherogenesis. LDL is taken up by vessel wall macrophages

and smooth cells to form foam cells as an important early part of atherosclerotic plaque development *[Sempos et al., 1990]*. Native LDL is taken up at a relatively slow rate by its receptor *[Schulman et al., 1990]*. However, modified LDL is taken up much more rapidly by the 'scavenger' *[Wolf et al., 1992]*. Modification of LDL appears to be important, and this modification may occur primarily via oxidation *[Steinberg et al., 1989]*. LDL-oxidation can be induced by free radicals produced by macrophages, smooth muscle cells, or endothelial cells *[Zimetbaum et al., 1990]*. Oxidized LDL may contribute to atherogenesis in other ways besides LDL accumulation with foam cells. oxidized LDL has cytotoxic properties and could promote endothelial injury and its propagation oxidized LDL appears to have chemoattractant properties for circulating monocytes and may contribute to monocyte accumulation within plaques. Paradoxically, oxidized LDL inhibits egress of plaque macrophages and may therefore enhance accumulation of monocyte-derived macrophages within plaques *[Yia-Herttuala et al., 1989]*. So, cellular and lipid contributors to atherogenesis must interact with one another, and LDL oxidation may be an important link.

The reported contribution of oxidized LDL to atherosclerotic plaque development suggests that inhibiting LDL-oxidation might reduce atherosclerotic plaque formation *[DeGraba et al., 1992]*. Probucol is a lipid-lowering medication with modest effects on LDL-cholesterol level, but it has been shown to substantially inhibit experimental atherogenesis *[Carew et al., 1987]*. Probucol has antioxidant effects and has been observed to

reduce endothelial cell and copper-induced LDL-oxidation. It is likely that the effect of probucol on atherogenesis are primarily mediated through its anti-oxidant effects *[DeGraba et al., 1992]*.

Atherogenesis: the lipid hypothesis

Simply stated an increase of cholesterol and saturated fats in diet, and subsequently in serum, parallels the association of lipids with atherosclerosis, primarily CHD, while for ABI, this relationship is less firm *[Tell et al., 1988]*. For lipoprotein, when analyzed, report correlations of strokes with elevated LDL, while showed an inverse relationship between HDL and strokes *[DeGraba et al., 1992]*. On fractionation of lipoproteins, reduction of HDL2 was found to be correlated inversely with strokes *[Guibilei et al., 1990]*. For HDL3, the fractional catabolic rate is faster in ABI, and for LDL, it is slower *[Sempos et al., 1990]*. This finding showing a reciprocal relationship between HDL and LDL metabolism corresponds with an increased LDL/HDL ratio but suggests that impaired, reverse cholesterol transport, mediated in part by HDL may be a significant factor in ABI pathogenesis *[Schulman et al., 1990]*.

In 1986 Zenker and his coworkers, reported an association of ABI with elevated lipoprotein (a) LP(a); LP(a) is a LDL molecule linked to along-chain polypeptide attached by Sulfhydryl bonds to apoprotein B.

The evidence suggested that replacing saturated fatty acids with polyunsaturated and monounsaturated fatty acids is beneficial in lowering total cholesterol and LDL *[DeGraba, et al., 1992]*.

Reduction of saturated fatty acids in a diet can also be achieved by replacement with a high carbohydrate intake. In addition to lowering cholesterol levels, this diet also promotes weight reduction *[Tell et al., 1988]*. Excess body weight has been associated with high very low density lipoprotein (VLDL) and moderate LDL increases, as well as low HDL levels *[Grundy 1990]*. Obesity promotes other atherosclerotic risk factors, such as hypertension and diabetes *[DeGraba et al., 1992]*.

Aneurysms

Aneurysms are localized segmental dilatations of the arterial wall. Depending on their shape and etiology, intracranial aneurysms can be classified into saccular (berry), dissecting, traumatic, fusiform (atherosclerotic), inflammatory (mycotic) and neoplastic (oncotic) aneurysms.

Fusiform (atherosclerotic) aneurysms are large, fusiform-shaped, associated with severe atherosclerosis, and occur mostly after the age of 60 years *[Garcia et al., 1992]*. These deformities commonly involve the basilar and internal carotid arteries, in particular, the cavernous segment of the latter. Fusiform aneurysms can enlarge and reach enormous size, compressing and distorting neighbouring cranial nerves and brain parenchyma.

Bleeding originating from these vascular deformities is uncommon *[Tomida et al., 1998]*. Infarcts involving the brain stem or diencephalon are the most common complications of atherosclerotic aneurysms *[Ruiz-sandoval et al., 1999]*.

Cerebral aneurysms of inflammatory origin are divided into infectious, usually referred to as mycotic aneurysms, and noninfectious aneurysms that are associated

with connective tissue diseases such as polyarteritis nodosa or giant-cell arteritis *[Garcia et al., 1992]*. Aneurysms at the size of bacterial lodgings are often associated with subacute bacterial endocarditis, and most commonly they coexist with cardiac valvular disease secondary to infections with gram-positive cocci *[Schold and Earnest 1978]*. True mycotic aneurysms (secondary to fungal infection) are less common than bacterial ones *[Ho, 1979]*. Destruction of the elastic lamina and tunica media by the infectious agents constitutes the basis for the aneurysmal formation *[Bohmfalk et al., 1978]*. Most bacterial aneurysms are small, less than 1.0cm in diameter, and involve peripheral arterial branches, in particular, the small branches of the middle cerebral artery located over the convexity of the cerebral hemispheres *[Katz et al., 1974]*. Fungal aneurysms tend to involve the large arteries at the base of the brain *[Goldman et al., 1979]*. The thinned arterial wall at the aneurysmal site may rupture easily, and this event results in a clinical picture similar to that provided by a ruptured saccular aneurysm, that is SAH or ICH *[Zimmerman and Seifert, 1998]*.

Intracranial neoplastic aneurysms secondary to tumor embolism to cerebral artery are rare, but their role in producing massive ICH has been well recognized *[Hill et al., 2000]*. The two most common neoplasms associated with neoplastic aneurysms are cardiac myxoma and choriocarcinoma *[Ho, 1982]*. Like mycotic aneurysms, most neoplastic aneurysms are small and involve peripheral, small branches of the cerebral arteries that are often buried in the cortical sulci *[Garcia et al., 1992]*.

Vascular malformations

Many vascular malformations (angiomas) of the central nervous system (CNS) result from the failure of the normal maturation of the vessels or persistence of vascular patterns normally present in the embryo *[Garcia et al., 1992]*. Despite their designation as angiomas, these lesions are not neoplastic. Vascular malformations of the CNS are traditionally classified into capillary telangiectasis, venous angioma, cavernous hemangioma and arteriovenous malformation, including the varix of the vein of Galen. Most vascular malformations are small, less than 2 or 3cm in diameter, and 90% are clinically silent *[Fujioka and Douville, 1992]*.

A capillary telangiectasis is typically a small (0.3 to 1.0cm) lesions that can not be visualized by angiography. Telangiectases are commonly found in the pontine base, they are less frequent in the cerebral white matter, where they look like clusters of petechiae. The vascular channels are separated from each other by normal brain parenchyma. Gliosis, mineralization and significant hemorrhage are very rare *[Reagan and Bloom, 1971]*.

Venous angiomas are the most frequently recognized type of vascular malformation found at autopsy, they are composed of groups of abnormal veins separated by either normal neural parenchyma or brain tissue with gliosis and ischemic injury *[Cabanes et al., 1979]*. Venous angiomas are not visualized during the arterial phase of angiography and are more frequent in the spinal cord and spinal meninges than in the brain *[Cawthorn et al., 1985]*.

A cavernous hemangioma is a well-circumscribed dark red to black compact mass of closely opposed sinusoidal type vessels that lack intervening neural parenchyma *[McCormick, 1966]*. Marked hyalinization and thickening of the component vessel walls are common. Calcification or even ossification can occur in some of the large cavernous hemangiomas that are more commonly found in deep-seated structures like the thalamus *[Garcia et al., 1992]*. Gross or microscopoic hemorrhages and gliosis of the adjacent neural parenchyma are common.

Arteriovenous malformation (AVM)

AVMs are the most significant vascular malformations of the CNS. Ninety-three percent of the AVMs are located supratentorially, the rest may involve cerebellum, brain stem or spinal cord *[Stein and Wolpert, 1980a]*. Microscpically, AVMs are composed of many large arteries, arterialized veins, and veins intermingled with islands of gliotic neural parenchyma and old hemorrhagic lesions. There is no recognizable capillary component in most AVMs. Sclerosis, thickening, and mineralization of the vessels' wall are common. Amyloid deposits in the vascular wall as well as thrombosis with recanalization are common. Segmental dilatations of the component vessels similar to those found in saccular aneurysms are frequently associated with AVM *[Stein and Wolpert, 1980b]*.

Arteriolosclerosis

The designation arteriolosclerosis applies to structural alterations involving small penetrating arteries and arterioles. The best-known causes of small blood vessel

disease (or arteriolosclerosis) are arterial hypertension, DM and aging. Perforating arteries develop accelerated atheromatosis or subintimal deposits of fibroblasts and lipid-laden macrophages *[Fisher, 1982]*.

The degenerative process in arterioles involves the tunica media where the smooth muscle fibers are progressively replaced by type IV collagen and plasma deposits. The resulting structural abnormality is called hyalinization *[Garcia et al., 1992]*. Other changes of arteriolosclerosis include fibrinoid necrosis. Microaneurysms affecting intraparenchymal blood vessels have been classified by Fisher in 1972 into four types, miliary saccular aneurysms, miliary aneurysms, fusiform miliary aneurysms and pseudoaneurysms. Miliary saccular aneurysms involve arteries with a diameter of 40 to 160um. Miliary aneurysms in lipohyalinosis can measure as much as 0.5 to 1.5mm in diameter and are not connected to the vascular lumen. Fusiform miliary aneurysms and pseudoaneurysms or "bleeding globes" that are formed by masses of erythrocytes and platelets held together by the fibers of the tunica adventitia.

Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a characteristic cellular mural thickening secondary to the deposition of an amorphous eosinophilic amyloid material stainable by Congo red *[Richardson, 1985]*. Topographically CAA is patchy and asymmetrical, but vascular deposits are more common in the parietal and occipital lobes than in the rest of the brain *[Vinters, 1987]*. The involved blood vessels,

particularly those located in the leptomeninges, frequently show additional deformities such as microaneurysm formation, double-barrel lumen fibrinoid necrosis, and obliterative intimal changes *[Mandybur, 1986]*.

CAA is associated with several clinicopathologic entities: cerebral hemorrhage, Alzheimer's disease, Down's syndrome, dementia pugilistica, cerebral microinfarcts, vasculitis, periventricular leukoencephalopathy, late post-irradiation encephalopathy, spongiform encephalopathy and vascular malformations *[Garcia et al., 1992]*. Tumor like amyloid deposits (amyloidoma) in the brain have been reported in a few cases *[Spaar et al., 1981]*.

CAA has been recognized as an important cause of nontraumatic ICH in aged persons with or without Alzheimer's disease *[Vinters, 1987]*. ICH in CAA patients are usually lobar hemorrhages, often involving the frontal and parietal lobes, and rarely involving deep ganglionic structures on cerebellum *[Ishii et al., 1984]*. Multiple, old, microscopic hemorrhages and microscopic infarcts are common in CAA, but SAH and subdural hemorrhages are rare *[Weisberg et al., 1990]*.

Cerebral angiitis

The terms arteritis, vasculitis and angiitis are used interchangeably because, in addition to arteries, veins and capillaries may be involved in some of the inflammatory conditions. Angiitis does not involve cerebral vessels alone. Cerebral angiitis may be caused by infectious agents, mechanical trauma, radiation, and toxins.

Cerebral angiitis may be associated with viral infections, in particular, herpes simplex, herpes zoster, cytomegalovirus and papovavirus. The most important angiitides, however, are the noninfectious systemic necrotizing angiitis affecting multiple organ systems *[Kadison and Haynes, 1988]*.

Polyarteritis nodosa: (PAN)

Classic PAN is a disease affecting small or medium-sized muscular arteries that characteristically involves the renal and visceral arteries but spares the pulmonary vessels. PAN affects young men more frequently than women; PAN is characterized by non specific systemic complaints such as low-grade fever, malaise weakness, leukocytosis, hypertension and hematuria. The etiology of PAN is unknown *[Sevage and Ng, 1988]*. The involved arteries show extensive leukocytic infiltration, including neutrophils, eosinophils and mononuclear cells as well as fibrinoid necrosis of the wall PAN include polymyositis, peripheral neuropathy, mononeuritis multiplex and 'Stroke' which is usually the result of either intracranial thrombosis or hemorrhage *[Garcia et al., 1992]*.

Takayasu's disease

Takayasu's disease, a form of granulomatous angiitis of medium and large arteries, involves primarily the aortic arch and its branches *[Hall et al., 1985]*. Microscopically, the lesion is characterized by mononuclear cell infiltration of the adventitia, perivascular cuffing of vasa vasora, granulomatous changes with multinucleated giant cells (Langhans cells) in the tunica media with foci of fibrinoid

necrosis. At a later stage obliteration may occur secondary to thickening and fibrosis of the wall. The luminal narrowing and obliteration are the morphologic basis for the clinical manifestations of the disease.

Patients exhibit no arterial pulsation and no marked drop in BP in the upper extremities, visual field defects, retinal hemorrhages, blindness and variable neurologic syndromes such as dizziness and stroke are also common *[Garcia et al., 1992]*.

Systemic lupus erythematosus (SLE)

SLE, a multisystem disease of autoimmune origin neurologic manifistations of SLE patients include psychiatric disorders, seizures, dementia, cerebral blindness, long tract signs, and several others. The symptoms have been attributed to angiitis with thrombosis and multiple petechiae. However, an autopsy study revealed no significant angiitis among SLE patients with neuropsychiatric disorders *[Blaustein, 1987]*. Instead, most cerebral lesions were attributed to brain infarcts of probable embolic origin *[Devinsky et al., 1988]*.

Ischemic lesions

Ischaemia or decreased blood flow, below the levels of autoregulatory compensation can be the consequence of hypotensive or hemodynamic crises and occlusive vascular disease involving any of the blood vessel types.

Ischemic lesions of the CNS having a hemodynamic origin are the consequence of episodic cardiac arrest, abrupt drops in systemic BP, shock, peripheral vascular

collapse and less frequently, cardiac dysrhythmias. The resulting parenchymal lesions can be of a very diverse nature and principally involve the cerebral cortical mantle, the basal ganglia, the cerebellar cortex, the cerebral white matter, the brain stem, the spinal cord, and various combinations of different sites at these components of the CNS *[Garcia, 1988]*.

After a cardiac arrest or a hypotensive crisis, the extent of the brain injury is influenced by the duration and severity (measured by the BP level upon recovery) of the ischemic event; additional factors influencing the outcome of a hypotensive ischemic injury include age of the patient (the younger the individual the longer the tolerance for ischaemia); body temperature (hypothermia protects neurons from the ischemic injury, whereas hyperthermia may have the opposite effect) *[Sekar et al., 1980]*, and serum glucose content (hypoglycemia at the time of the ischemic event is said to protect the ischemic brain by limiting the rate of production of lactic acid) *[Garcia and Anderson, 1991]*.

As seen in imaging studies, the brain lesions attributed to ischaemia of hypotensive origin are almost always bilateral and relatively symmetrical regardless of their location in the CNS. Some hypotensive ischemic lesions may have a hemorrhagic character *[Garcia et al., 1992]*. This is explained by the presence, in the involved segment of the brain, of numerous petchiae that almost always remain confined to the gray matter structures.

Systemic hypoperfusion of the brain has also been proposed as one of several mechanisms that may induce a diffuse lesion in the periventricular white matter of the cerebral hemispheres *[Garcia and Brown 1992]*. Leuko-araiosis, or areas of decreased density on either CT scanning or magnetic resonance imaging (MRI) of the head, is a common finding among persons older than 65 years.

Brain infarcts secondary to focal ischaemia

Brain infarcts may be the consequence of either embolism or thrombosis.

The latter is thought to be secondary to local vascular disease; in a significant percentage of cases, the causes of intracranial vascular occlusions responsible for brain infarcts remain undetected *[Sacco et al., 1989]*. Many patients with vascular occlusion of unknown etiology may have hematologic abnormalities that promote intravascular coagulation, such as antiphospholipid antibodies *[Briley et al., 1989]*.

Embolic brain infarcts

Two common sources of embolism to the brain are left-sided chambers of the heart (especially after a transmural MI) and the origin of the internal carotid artery. The mitral and aortic valves can be the sites where vegetations form in patients who have hypercoagulable states. The classical example being a patient with an adenocarcinoma of the pancreas who develops multiple thrombi in both veins and cardiac valves. Valvular vegetations in these patients are usually made of fibrin and

are sometimes called "marantic vegetations" *[Garcia et al., 1992]*. Marantic endocarditis is an inappropriate designation, the preferred name is nonbacterial thrombotic vegetations. Patients with SLE are prone to develop vegitations of a similar type that are sometimes called Libman-sacks vegetations. Congenital valvular defects and systemic infections can also be the precipitating factors for the formation of bacterial-infected vegetation, this results in the classical condition of bacterial endocarditis. The origin of cerebral emboli among patients with AF is disputed; postmortem studies of these patients seldom show mural thrombi in the atrial appendages of the heart *[Garcia et al., 1992]*.

Artery-to-artery embolism frequently results from the detachment of mural thrombi from the internal carotid artery, at the site of an ulcerated atheromatous plaque. In such cases, the material occluding small branches of the ophthalmic or middle cerebral arteries is composed primarily of platelets and fibrin *[Swanson et al., 1990]*. Emboli to the cerebral hemispheres commonly lodge at the junction between cortex and white matter and preferentially involve the bottom of the sulcus rather than the rest of the gyrus *[Garcia et al., 1992]*. Many brain infarcts of embolic origin are hemorrhagic, presumably because the ischemic tissue is often reperfused when the embolizing material lyses and the occluded vessel is reopened *[Benesch et al., 1997]*. Another common feature of embolic infarcts is their relatively small size (usually less than 2.0cm in diameter) and their multiplicity within a single arterial territory *[Futrell et al., 1991]*.

The inflammatory response by polymorphonuclear leukocytes at the site of an embolic infarct is usually more pronounced than it is at sites of thrombotic infarcts, this is reflected in a relatively high increase in the neutrophil count in the cerebral spinal fluid, which, in addition, may also contain numerous erythrocytes *[Garcia et al., 1992]*.

Thrombotic arterial infarcts

The classical example of thrombotic arterial brain infarct is seen in the hypertensive, diabetic patient who has severe atherosclerosis of the basilar artery; at the site of extreme narrowing.

The vessel develops a thrombus that completely occludes the artery, a similar set of circumstances may lead to the thrombotic occlusion of middle cerebral artery *[Bougouslavsky et al., 1991]*. As studied serially in experimental animals, occluding an intracranial artery results in an instantaneous drop in the local CBF and loss of function of tissues supplied by the occluded vessel. For the next several minutes, perhaps hours, the tissue changes included by this type of ischaemia can be detected only with the microscope; some of these changes may be of a reversible nature *[Sundt et al., 1981]*.

Reperfusion can be complicated by massive intracerebral bleeding at the site of an incipient brain infarct. This phenomenon probably explains one of the well documented complications of carotid endarterectomy, in few patients undergoing this operation, the postoperative period is complicated by a massive, usually fatal, ICH *[Loes et al., 1990]*.

It was found that approximately 2 to 3 hours after the occlusion of an artery, the brain lesion becomes irreversible *[Crowell et al., 1981]*. The sharply demarcated areas of coagulative necrosis that occur after occluding a major brain artery are not visible even in autopsy specimens before 12 to 24 hours after the occurrence of the neurologic deficit *[Dereski et al., 1991]*.

An initial wave of infiltration by neutrophils begins about 1 to 4 hours after the arterial occlusion; this is followed some 8 hours later by a second massive increase in the number of neutrophils visible within the ischemic territory. The presence of macrophages, first noted on the fourth day, becomes more obvious by the end of the tenth day. *[Garcia et al., 1992]*.

Brain infarcts that are reperfused at some critical, but as yet undefined, time period adopt a hemorrhagic character; these lesions are sometimes called red infarcts, as opposed to the pale, bland, or anemic infarcts lacking a grossly visible hemorrhagic component *[Boon et al., 1994]*. Two types of hemorrhages have been described in brain infarcts: type I consists of numerous punctate hemorrhages that generally remain confined to the gray matter structures and do not result in either tissue swelling or added deterioration of the neurologic deficit; type II hemorrhage in an arterial brain infarct is a large collection of blood frequently involving the white matter structures and dissecting the surrounding tissues in an unpredictable fashion *[Bougouslavsky et al., 1991]*. This type of hemorrhage frequently extends into the ventricular cavities, the extension of the subarachnoid space through the

cortical mantle occurs less frequently *[Garcia et al., 1992]*. The occurrence of type II hemorrhage is reflected in an abrupt added deterioration of the neurologic deficit; and the abrupt extension of the bleeding into the ventricles can be lethal *[Garcia et al., 1988]*.

The ultimate fate of brain tissues made necrotic by an arterial occlusion is the reabsorption of the dead cells by macrophages leading to the formation of a fluid-filled cavity at the site of the original brain infarct. The time necessary for a brain infarct to become a cavity cannot be predicted accurately, it is assumed that the larger the lesion the longer it will take for cavitation to develop. Large infarcts in the territory of the middle cerebral artery may take several months before they convert into a cavity *[Garcia et al., 1992]*.

Tissue responses are primarily dependent on the severity of the ischemic event *[Lassen et al., 1978]*. Severity can be influenced by two main factors: the level to which the local CBF falls and duration of the ischemic event. Both factors are influenced by BP changes (since autoregulation is lost at the site of the infarct) and by the local conditions dependent on the collateral vessels *[Marcoux et al., 1982]*.

Lacunar infarcts

The designation lacunar infarcts is applied to destructive brain lesions of presumed ischemic origin having a maximum diameter of 1.5cm, the vessels whose occlusion is thought to be responsible for the lacunar infarct (or lacune) are penetrating arteries or arterioles

generally having a caliber of less than 200um *[Fisher, 1982]*. The name lacune is derived from an astronomical term (lacuna) meaning a black hole in outer space. Because of their small size lacunar infarcts are not detectable by in vivo imaging studies until the time when they become cavitary *[Garcia et al., 1992]*.

Lacunes are most commonly found at these anatomic sites: the basal ganglia, thalamic nuclei, base of the pons, centrum semiovale, and less frequently, cerebral and cerebellar cortices *[Futrell and Millikan, 1990]*.

The etiology of vascular disease associated with lacunes is generally attributed to the consequences of arterial hypertension and DM on small penetrating vessels; these are thought to become occluded as a result of progressive mural thickening and hyalinization *[Makino et al., 2000]*. A second possible mechanism for the development of lacunes is embolism from the internal carotid artery *[Garcia et al., 1992]*. The histologic feature of lacunes are thought to be comparable to those of other brain infarcts.

Brain lesions secondary to sinus/venous thrombosis

Occlusion of an intracranial vein may have disastrous effects because there are no collateral connections among cerebral veins and because close to 70% of the intracranial blood is contained within the veins and sinuses of the brain *[Jorgensen et al., 1995]*.

Three varieties of lesions have been recognized among patients with intracranial sinus thrombosis. the first and most common lesion is the development of SAH accompanied by massive swelling of the cerebral

hemispheres that may lead to compression of the cerebral ventricles; this type of lesion has been observed among children with superior sagittal sinus thrombosis.

The condition of sinus thrombosis constitutes an emergency that requires prompt medical treatment with agents that prevent additional thrombus formation.

Surgical intervention to attempt recanalization of the sinus has not been successful *[Einhaupl et al., 1990]*. The second type of lesion consists of a localized area of brain softening (or infarct) having a topographic distribution that overlaps two or more arterial territories.

Characteristically the lesion is markedly edematous and accompanied by large hemorrhages that are profuse in the white matter as well as in the cortex or basal ganglia *[Garcia et al., 1992]*.

A third type of brain lesion is more diffuse, multifocal, and subtle; its detection usually requires microscopic evaluation of the involved tissues. It consists of the plugging of numerous capillaries and venules by thrombi composed of platelets, fibrin and erythrocytes. This type of event has been observed in patients dying during acute sickle cell crises *[Garcia, 1990]*.

At the microscopic level, four features differentiate venous lesions from infarcts of arterial origin. First, venous infarcts have abundant signs of cellular and extra-cellular edema, including frequent "plasma lakes". Second, a common feature of venous infarcts is the presence of abundant neutrophils distributed in sheets, instead of perivascular cuffs commonly seen in lesions secondary to

arterial embolism. Third, characteristic of venous infarcts is the relative preservation of the neuronal morphology, even in areas where extensive edema and neutrophil accumulation, as well as hemorrhage, may be present. Fourth, coagulation necrosis is absent in venous infarcts *[Garcia, 1990]*.

Subcortical leukoencephalopathy, hypertensive encephalopathy

Structural alterations involving the white matter that surrounds the lateral ventricles are seen on CT scans with increasing frequency after the age of 65 *[Garcia et al., 1992]*. The designation of subcortical leukoencephalopathy seems preferable because it does not imply a specific or single etiologic mechanism. It has been suggested that the structural alterations of the long, penetrating, radial arteries that supply the white matter, commonly known as arteriolosclerosis, are the most frequent etiologic cause for subcortical leukoencephalopathy. Arteriolosclerosis is common among persons with arterial hypertension, DM, and advanced age *[Kannel, 1996]*.

On the microscopic level a variety of structural alterations have been described, these include loss of myelin sheaths, loss of axons, proliferation of astrocytes, infiltration by lipid-laden macrophages, cavitation and various degrees of disappearance of oligodendrocytes *[Garcia et al., 1992]*.

Intracerebral hemorrhage (ICH)

Spontaneous hemorrhage is a phenomenon particularly important in the CNS and its coverings primary ICH is

defined as a non traumatic hemorrhage within the parenchyma of the brain *[Ruiz-Sandoval et al., 1999]*. Some authors have attempted to differentiate brain hemorrhage from brain "hematoma" the hemorrhage being a deep-seated, poorly circumscribed accumulation of blood extending to the ventricles. A "cerebral hematoma" in contrast, would be a superficial and more localized accumulation of blood, that reaches the cerebral surface, but does not extend to the ventricles *[Weisberg et al., 1990]*. However, there are many exceptions to those broad categories and the terms "cerebral hemorrhage" and "cerebral hematoma" are used interchangeably.

Etiology and pathogenesis

Approximately 10% of strokes are ICH of which primary ICH (PICH), defined as spontaneous ICH not attributed to an underlying cause is a subset *[Bogousslavsky et al., 1988]*. PICH is more often a devastating disease than ischemic stroke *[Jorgensen et al., 1995]*. Among survivors, the rate of stroke recurrence after PICH has not been studied extensively. In patients with recurrent hemorrhage, lobar location of hemorrhage is a known predictor of recurrence *[Hill et al., 2000]*.

CAA and hypertension are two of the major known risk factors of PICH *[Bahemuka, 1987]*. CAA hemorrhage usually affects patients in their eight decade and is typically lobar, rarely involving the deep subcortical nuclei *[Ruiz-Sandoval et al., 1999]*.

Hypertension is present in only 50% of patients with PICH in modern series. However, treatment of hypertension has had a major impact on the incidence of PICH over the past 50 years *[Hill et al., 2000]*.

Mechanisms that may explain the ICH associated with hypertension, include rupture of microaneurysms, arteriolosclerosis, necrosis of vessels, and rupture of veins or dissecting anuerysms *[Lee et al., 1990]*.

Aneurysms were found with greater frequency in hypertensive patients (approximately 50%) compared to normotensive individuals (5-8%) *[Garcia et al., 1992]*. In 1999, Wong suggested that hypertension is associated with significantly lower mortality rate in patients with ICH. It was likely that non hypertensive patients had other underlying causes such as amyloid angiopathy or occult angioma which might be more severe and cause worse outcomes *[Caplan, 1992]*.

It has been proposed that the interaction of high diastolic BP and low cholesterol levels weakens the endothelium of the intracerebral arteries, resulting in hemorrhagic stroke in the presence of hypertension *[Ruiz Sandoval et al., 1999]*.

Lobar hemorrhages occur in the subcortical white matter of the cerebral hemispheres or the centrum ovale *[Tuhrim et al., 1995]*. Approximatel 30% of lobar ICH are believed to be secondary to hypertension, other causes, such as eclampsia or amyloid angiopathy, may include ICH in this location at a more frequent rate than hypertension

[Meschia et al., 1999]. In 2000, Hill and his coworkers suggested that lobar location of the index hemorrhage was the only significant predictor of recurrence and increased the risk of recurrence by a factor of 3.8.

It is suggested that recurrent hemorrhage due to hypertension may be more common than previously believed *[Ruiz-Sandoval et al., 1999].*

Interestingly, patients with PICH were slightly more likely to be readmitted to the hospital with ischemic cerebrovascular disease than with recurrent hemorrhage. This has clear implications for management of seconary prevention *[Meschia et al., 1999].* Anticoagulant therapy may be contraindicated in patients with lobar hemorrhage.

Recent data support the concept that patients with amyloid angiopathy or leukoaraiosis are much more likely to develop ICH while undergoing anticoagulant therapy *[Gorter, 1999].* The use of antiplatelet therapy in patients with past ICH remains controversial.

Acetylsalicylic acid may increase the risk of ICH *[He et al., 1998].* However, the equivalence of rates of recurrence of both ischemic cerebrovascular disease and ICH in this group of patients suggests that the PICH is a risk factor for ischemic stroke. Therefore, attention to the known ischemic stroke risk factors (in addition to hypertension), such as hypercholestrolemia, is probably important. It remains uncertain whether antiplatelet agents should be used as a primary ischemic stroke prevention in this group of patients, but this is potentially a testable

hypothesis for a randomized trial *[Hill et al., 2000]*. In 2000, Makino and his colleagues suggested that, the use of antiplatelet agents may not be effective in the primary prevention of stroke in treated hypertensive patients. They also suggested that the use of anticoagulant and antiplatelet agents was more frequent in the stroke group due to high prevalence of AF and other cardiovascular complications.

It has been shown that warfarin prevents stroke in patients with AF, however, there was no evidence of primary prevention of stroke with acetylsalyclic acid *[Wolf, 1998]*.

ICH with secondary etiology (Table 1)

Coagulopathies and myeloproliferative disorders are also associated with spontaneous ICH. ICH can occur in patients with disseminated intravascular coagulation (DIC) *[Garcia et al., 1992]*. In this condition, ICHs are a manifestation of a systemic bleeding disorder and the hemorrhage are seldom restricted to the brain. ICH also occurs in hemophiliacs, especially in patients who have very low levels of circulating factor VIII *[Martinowitz et al., 1986]*.

ICHs are important complications of leukemia; and a hemorrhagic "stroke" can be the initial manifestation of the leukemia *[Garcia et al., 1992]*.

Table 1: ICH with secondary etiology

Causes of secondary ICH
AVM or aneurysm
Hemorrhage into neoplasm*
Anticoagulation
Hemorrhage into infarct *
Thrombocytopenia *
Postthrombolytic therapy
Trauma
Moyamoya disease
Acute hepatic failure
Leukemia
Hyperperfusion syndrome after endarterectomy
↑ aPTT of undetermined etiology
Other

AVM = indicates AVM; aPTT = activated partial thromboplastin time.
Platelets <150.
Other: one of venous sinus thrombosis, after biopsy for cytomegalovirus encephalitis, hemorrhage into a benign cyst; polycythemia rubra vera, Waldenstrom's macroglobulinemia, acute hemorrhagic leukoencephalitis, hemophilia type A and HELLP syndrome *[Hill et al., 2000]*.

Subarachnoid hemorrhage (SAH)

SAH describes bleeding into the subarachnoid space where blood comes in direct contact with the cerebrospinal fluid *[Zimmerman and Seifert, 1998]*. The extent and site of the hemorrhage depends on the cause of bleeding. In most cases of ruptured aneurysms, the bulk of the hemorrhage is collected at the base of the brain. SAH localized to the cerebral convexity are more common in cases of ruptured AVMs *[Sobey and Faraci, 1998]*. Large collections of blood are necessary to produce arachnoidal rupture and extension of blood into the subdural space. Large collections of blood in the subarachnoid space may produce ICH *[Garcia et al., 1992]*.

The presence of blood in the subarachnoid space elicits an inflammatory and fibrotic reaction. Approximately 4-16 hours after the hemorrhage, an inflammatory reaction consisting mainly of neutrophils becomes evident in the meninges. Non traumatic SAH constitutes approximately 6-8% of all strokes (or abrupt focal neurologic deficit) *[Kurtzke, 1985]*.

Cerebral vasospasm (CVS) is a major cause of morbidity and mortality after SAH, due to rupture of the aneurysm *[Kassell et al., 1985]*. Despite intensive efforts to understand the pathogenesis of CVS, the biological processes leading to arterial narrowing remain unclear. In the past few years, increasing evidence has shown that natriuretic peptides (NPs), very potent vasodilators, are responsible for diuresis, natriuresis and hyponatremia in patients with SAH *[Tomida et al., 1998]*. Three types of NPs have been described to date. The atrial natriuretic peptide (ANP), first discovered, is mainly produced in the right atrium in response to hypovolemia and increase in the cardiac preload *[Kangawa and Matsuo, 1984]*. The brain natriuretic peptide BNP is produced mainly in the cardiac ventricles. Although primarily of cardiac origin, the BNP has been shown to be produced also in the hypothalamus, so its release may be induced by pathological processes involving this region *[Sviri et al., 2000]*. The C type of natriuretic peptide is mainly released from the vascular endothelium in response to injury and inflammation *[Chen and Burnett, 1998]*. All types of NPs have been demonstrated to be very potent vasodilators and natriuretic.

It was first speculated that ANP which was found to be elevated in the cerebrospinal fluid and plasma of patients with SAH, might be responsible for profound diuersis and natriuresis *[Nelson et al., 1984]*. Berendes et al. in 1997, provided convincing evidence that the BNP may be related to hyponatremia associated with natriuresis after SAH. Sviri et al. in 2000, demonstrated that BNP plasma levels increase progressively and significantly during the first 2 weeks in patients with severe CVS after aneurysmal SAH compared with patients with non symptomatic CVS or without vasospasm. These findings raise the question of the role of NPs, particularly BNP in the pathogenesis of CVS. Also, they suggested that, despite of some protective effects, such as vasodilatation, BNP secretion may exacerbate blood flow reduction due to arterial vasospasm and eventually result in ischemic brain damage.

CHAPTER 3

DIAGNOSIS

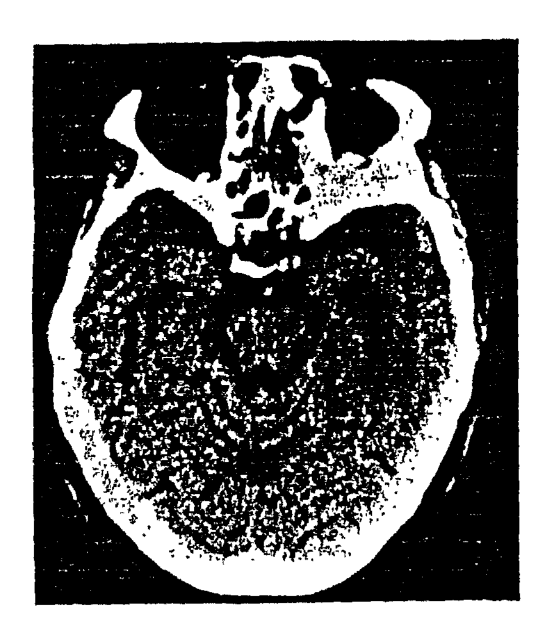
Faced with a stroke, the physician must determine the cause, estimate the severity, consider the possibility it may progress or recur, and seek ways of stabilizing or reversing it. Because the possibility of worsening or recurrence is paramount, speedy efforts should be made to arrive at a diagnosis of stroke mechanism *[Kaps and Link, 1998]*.

The evaluation of suspected stroke should include blood chemistries to search for hypoglycemia, hyponatremia, hypernaturema and renal failure. Additional routine studies should include an INR if the patient is being with oral anticoagulant, ECG if AF is suspected and a chest x-ray if the patient has fever. Methods of diagnosis can be summarized as brain imaging, transcranial Doppler and angiography.

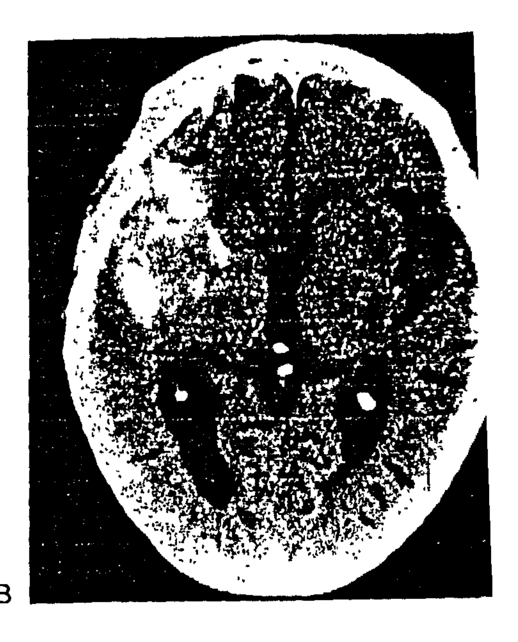
Brain imaging (Fig.1,2,3)

In most hospitals the first step taken with laboratory test is to try to image the injured site by CT or MRI. If neither is available, estimates of risk factor analysis and clinical assessments of syndrome greatly help but can not substitute with certainly for brain imaging *[Mohr, 1992]*.

The initial scan should separate hemorrhage from ischaemia or infarction. For the CT scan, high-density signal attenuation (about 80 HU) points to hemorrhage, low-density to ischaemia, the reverse the case for MR scanning using the most frequent method of the long T2 sequence *[Savoiardo and Grisoli, 1992]*.

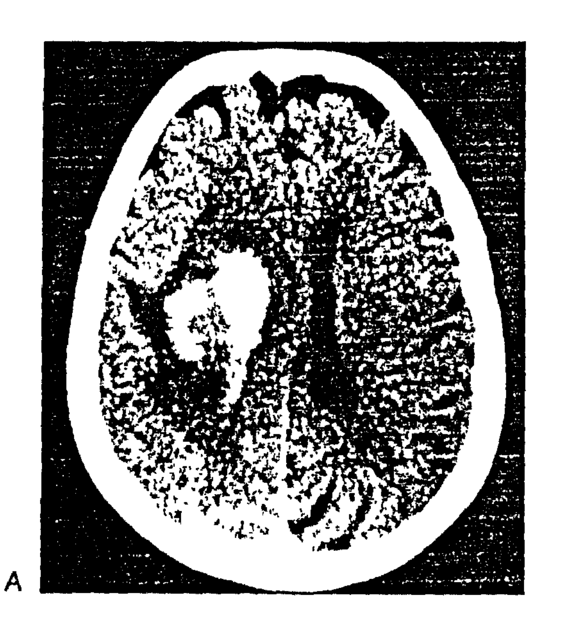


A

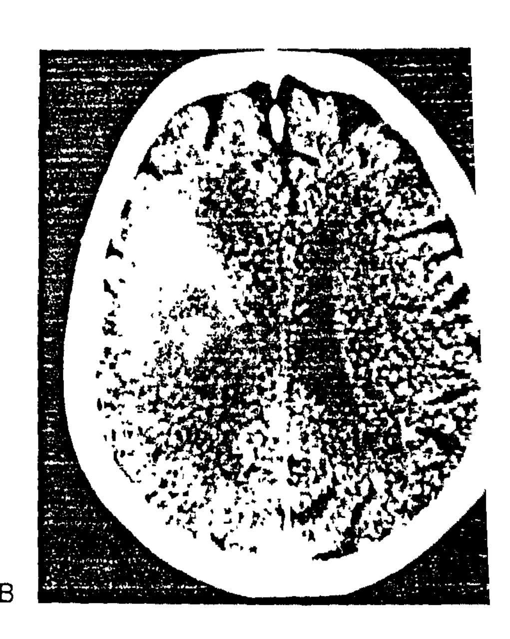


B

Fig.1: Computed tomography scans in a hypertensive patient: (A) Lacunar infarct in right upper pons; (B) Lacunar infarcts inboth thalami and both lentiform nuclei.



A



B

Fig.2: (A) Hematoma 6 days after stroke; (B) Same hematoma 30 days after stroke. Despite the densiy change, the size of he hematoma and its mass effect are unchanged.

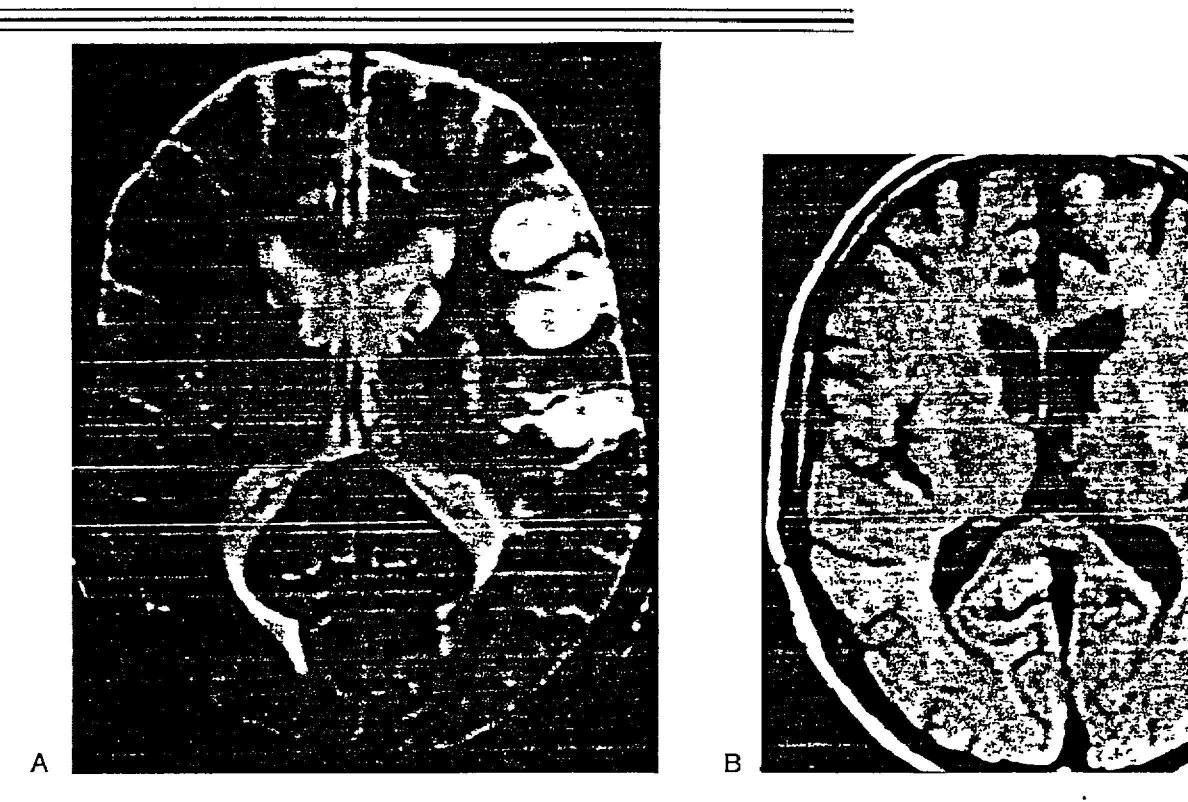


Fig.3: (A) T2-weighted MR 27 hours after stroke showing acute hemispherl convexity infarction; (B) T1-weighted MR at 27 hours showing faint changes over the same site showing prominent changes on T2

In CT scanning, the high-density abnormality from parenchymatous hemorrhage is usually rather in the acute stage, and gradually loses its density over a week in the smaller hemorrhage, persisting as long as months for the larger or more intense hemorrhage *[Grond et al., 1997]*. Infarction followed by hemorrhagic transformation is more easily recognized when it is confined to the cerebral surface, but it may mimic the findings of hematoma, making a certain differential diagnosis difficult *[Von Kummer et al., 1999]*. One exception, a finding that seems specific for hemorrhage, is the pooling of blood found in some labor hemorrhages *[Zilkha, 1983]*. Hemorrhagic infarction can be inferred when the lesion lies in the territory of a single surface branch or is limited to the cortex in ribbon like fashion, but even these findings have been mimicked in lobar hemorrhage. MR scanning shows the same uniform density as does CT for hematomas, but suffers the same problem as CT in failing to separate dense hemorrhagic infarction from hematoma in all cases. MR is more sensitive than CT in showing minor examples of hemorrhagic infarction *[Mohr, 1992]*.

On CT scan, infarction appearing as a low-density focus occurs as early as 3 hours, but more often does not make an appearance before 6 hours *[von Kummer et al., 1999]*. After 12 hours almost half the cases are positive, and certainly after 48 hours, reaching a plateau within 3 days in more than 60% of cases. Completed studies suggested that both CT and MR are comparable for detecting the lesion in the earliest hours, and neither have much success before about 3 to 4 hours from onset *[Mohr, 1992]*.

In the cerebrum, the topography of the CT or MR abnormality may assist in differentiating distal infarction due to large-artery thrombosis from infarction attributed to embolism: the former is higher over the convexity and usually spares the sylvian region, while the latter conforms more to the territory supplied by one or more cerebral surface branches *[Powers and zivin, 1998]*. Small surface infarcts are not always easily visualized on CT scan, since they may be hidden in the gyral pattern of the convexity, MR is a better tool *[Grond et al., 1997]*. In late CT scanning, some low-density lesions are the late effect of parenchymatous hematoma, a diagnosis more easily made by MR where the residual methemoglobin leaves a permanent signal change. A high-density mass in the stem of the middle cerebral artery strongly suggests embolism, but this occurs infrequently *[Savoiardo et al., 1987]*.

MR scanning offers a clear advantage over CT for imaging flowing blood, which appears black on the MR, allowing a diagnosis with high degree of accuracy *[Nussel et al., 1991]*. This physiologic effect allows the diagnosis of AVM in ways difficult for CT scan, which relies on hemorrhage, calcification, or contrast enhancement to suggest the diagnosis, even though it is positive in upto 80% of cases *[von Kummer et al., 1999]*. MR has also become the tool of choice for the demonstration of cavernous angiomas, which have a low signal center and high signal rim commonly called a “tiger eye”. These small angiographically occult lesions may cause brain hemorrhage.

MR may also demonstrate the thrombosed dome of a recently ruptured aneurysm, a difficult imaging feat rarely achieved by CT scan *[Mohr, 1992]*.

Both CT and MR can document deep infarcts. MR imaging smaller lesions than those seen by CT, especially in the basal ganglia and thalamus *[Zivin, 1997]*. MR is preferred over CT for the smaller infarcts deep in the brain and for those in the brain stem *[Savoiardo et al., 1987]*. Yet the mere imaging of these smaller lesions does not settle the mechanism, whether thrombolic or embolic *[Mohr, 1983]*.

The ideal diagnostic tool for the management of acute ischemic stroke should be non invasive, provide information on the severity and extent of hypoperfusion, and assess the proportion of already irreversibly damaged tissue *[Grond et al., 2000]*.

Hypoattenuation on CT indicating ischemic edema was frequent (56%) and highly predictive of definitive infarction (positive predictive value of 100%) *[Ianotti and Hoff, 1983]*.

Patients with a normal CT should not be excluded from aggressive therapy. Because of the delayed appearance of ischemic edema, negative CT findings are of limited predictive value at that early stage (<3 hours) *[Grond et al., 2000]*.

Flow studies can provide information on the severity and extent of hypoperfusion but not on tissue integrity. Flow changes are present at symptom onset, but their extent may vary in the dynamic process of cerebral

ischaemia. In the very early phase, the area of hypoperfusion is equivalent to the area of tissue at risk, and its assessment may be helpful in therapeutic decisions. Whether or not hypoperfusion leads to necrosis depends not only on severity but also on duration of hypoperfusion. *[Heiss et al., 1998]*.

They also found that even critically hypoperfused tissue could be salvaged by early reperfusion. Parenchymal hypoattenuation and cortical effacement indicating brain swelling might represent 2 different entities with different prognostic significance where as parenchymal hypoattenuation is highly predictive of irreversible tissue damage, the fate of swollen brain tissue has not been sufficiently analyzed. Area with focal swelling may be salvaged from infarction, but in other cases they may become irreversibly damaged despite thrombolytic therapy *[Heiss et al., 1999]*.

In the future, CT may be replaced by new MRI technology. Combined diffusion, and perfusion-weighted imaging might be able to outline irreversible tissue damage and to suggest the existence of a penumbra *[Jansen et al., 1999]*. However, diffusion changes were recently reported to be present and also reversible in patients with transient ischemic attack *[Kidwell et al., 1999]*. Therefore, more basic and clinical work needs to be done before this technique can be used reliably in clinical routine *[Powers and Zivin, 1998]*. In addition, in the near feature, this sophisticated and expensive technique will not be available in most community hospitals, which currently treat the majority of stroke patients.

Duplex and transcranial Doppler

The presence and location of arterial occlusion help to determine likelihood of recanalization with thrombolysis as well as underlying stroke mechanism, secondary stroke prevention options and prognosis. In experienced hands, the duplex and Transcranial Doppler (TCD) methods may provide useful information within minutes, adding to the assessment of acute stroke *[Mohr, 1992]*. In a setting of occlusion, in the early hours after stroke, before brain imaging can demonstrate the changes of infarction, duplex Doppler may disclose high-grade stenosis of a carotid or vertebral artery. TCD is a non-invasive method that can be used to identify intracranial and extracranial arterial occlusion *[Willerdink et al., 1997]*.

Specific TCD findings are common with major arterial occlusion and can be used to broaden diagnostic batteries and improve the predictive value of noninvasive screening in stroke patients. TCD findings useful to localize anterior circulation occlusion include collaterals, abnormal wave forms or velocities and flow diversion to perforators *[Demchuk et al., 2000]*.

A proximal occlusion on TCD was found in 69% of thrombolysis-eligible patients. In 26% of all patients, TCD provided further relevant information that, in addition to antiography, helped to refine the severity of a stenosis and determine stroke pathogenesis. Emergent TCD is both sensitive and specific in determining arterial occlusion and stenosis in acute cerebral ischaemia *[Alexandrov et al., 1999]*.

Angiography (Fig.4)

Angiography remains the preferred tool for demonstrating aneurysms and vasospasm, for easily diagnosing AVM, and for separating embolism from large artery thrombosis *[Mohr, 1992]*. Many embolic occlusions are quite transient, forcing a plan for prompt angiography if a diagnosis of occlusion due to embolism is to be confirmed *[Babikian et al., 1997]*. The search for a source of embolism is a separate issue from documenting the occurrence of brain embolism. In the case of the former, conventional monitoring of arrhythmias, blood cultures and ECG usually take days. If delayed until the results of these tests are complete, angiography could yield a negative study *[Mohr, 1992]*. Digital subtraction angiography, a technique which underwent rapid development in the last decade, is fast being eclipsed in some centers by MR angiography, which has almost matched conventional angiography in estimation of disease at the carotid bifurcation, and is rapidly developing the potential to estimate blood flow and other time-based changes *[Tarnawski et al., 1991]*. In both digital and MR angiography, the circle of Willis and the basilar artery, their main branches, and many of the large surface vessels can be imaged well enough to determine if some are occluded *[Cline et al., 1991]*.

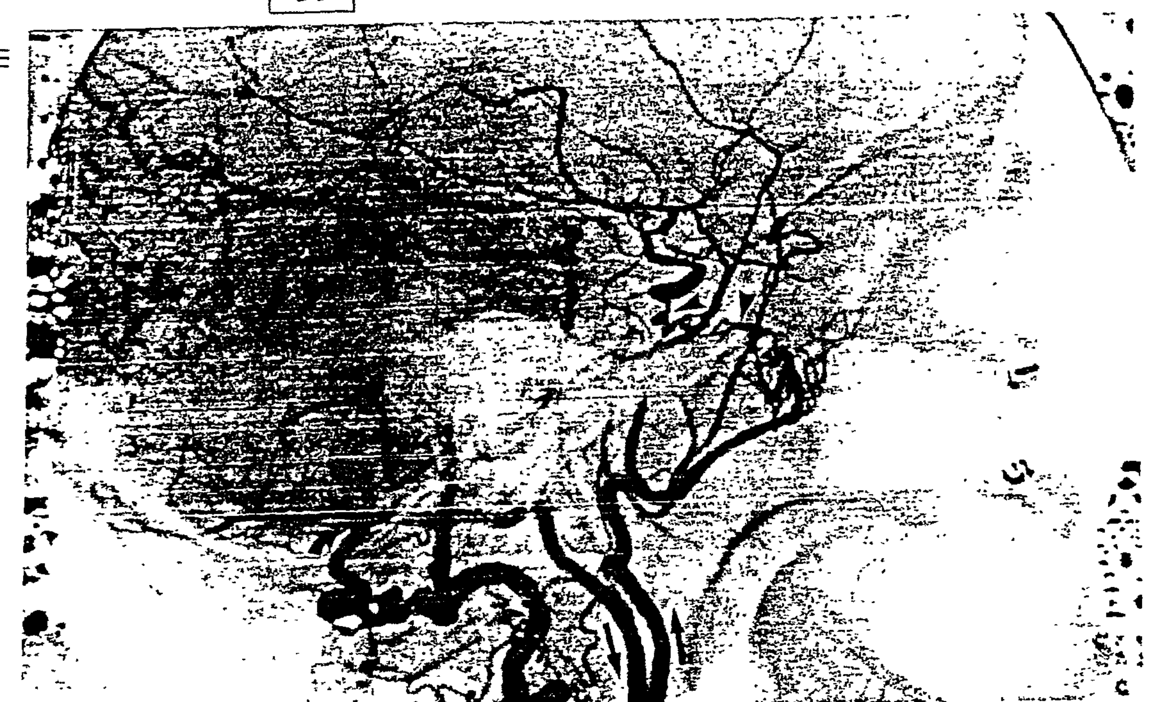


Fig.4: Patient with left common carotid occlusion (not shown). Left vetebral agiogram, lateral view, enlrged muscular branch of the vertebral artery (curved arrow) retrogradely fills the occipital branch of the extrnal carotid artery (arrow downward) to reconstitute the exernal (arrow upward), which then reconstitutes the cavernous and upraclinoid internal crotid artery via branche incuding the artery of the foramen rotundum (arrowheads).

Studies of blood flow and metabolism

Xenon computed tomography and single photon emission computed tomogrpahy:

Xenon computed tomography blood flow imaging is gaining acceptance and has been supplemented by single photon emission computed tomography (SPECT) *[Hanyu et al., 1990]*. Both demonstrate both local and distant functional effects after stroke, and some have shown effects on resting flows remote from the site of infarction. Applied quickly after infarction, the deficit in local flow may be evident before the tissue signal changes appear on CT or MR scan. Neither technique separates, hemorrhage from infarction. It remains uncertain if these methods will predict the potential for clinical recovery *[Demeurisse et al., 1983]*. A compination of TCD and CBF has been helpful in taking the course of vasospasm in SAH *[Jakobsen et al., 1990]*.

Positron Emission Tomography

Positron emission tomography (PET) scanning has demonstrated its power in documenting the functional metabolic response of the brain to focal infarction, but its availability remains limited *[Mohr, 1992]*. It remains the best method for demonstrating viable tissue in carotid occlusive disease and has been able to demonstrate the remote effects of infarction, some spread over wide areas and some explained as transsynaptic depression or diaschesis *[Kiyosawa et al., 1990]*.

Transient ischemic attacks

It is only after the symptoms have faded that a diagnosis of TIA is justified. In the acute symptomatic phase, the approach is that of an acute stroke *[Kidwell et al., 1999]*. Symptoms may fade or entirely disappear, yet brain imaging demonstrates a recent ischemic lesion. The old definition of TIA as any neurologic deficit resolving within 24 hours is out of date *[Mohr, 1992]*. The actual duration of a brief ischemic event is typically measured in minutes, not hours. When symptoms have lasted longer than 1 hour there has been a higher frequency of brain lesions found than when the symptoms have lasted for minutes *[Jansen et al., 1999]*.

After it is certain all symptoms have disapeared, investigation of a TIA is directed at underlying disease, which may predict the risk of recurrence in the same or different vascular territory *[von Kummer et al., 1999]*.

By habit and because of a surgical option for therapy, TIAs are often equated with the surgically correctable disease in the neck at the carotid bifurcation. However, TIAs may occur in territories remote from the carotid. For these affecting the carotid territory, duplex and TCD should suffice to demonstrate whether high-grade stenosis or occlusion exists and whether there is indication of the development of some vascular collateral *[Alexandrov et al., 1999]*. Embolism may account for many TIAs yet some may be explained by "distal insufficiency" in the far feilds of the middle cerebral artery or in the border-zone between the middle and anterior cerebral arteries *[Valton et al., 1997]*. This suprasylvian location would be

expected to produce a clinical deficit involving the forearm and hand. There has been a high frequency of stereotypic neurologic deficits in a given patient suffering repeated TIAs *[Mohr, 1992]*.

PET and SPECT can determine whether the brain supplied through the stenosis or by collaterals around the stenosis or occlusion suffers from inadequate flow or "misery perfusion syndrome", which has been shown to be surgically revesible in some instances *[Baron et al., 1981]*. In the even more severe state of distal intracranial internal carotid artery stenosis with abundant collaterals associated with the moyamoya disorder, hyperventilation has been shown to precipitate focal symptoms *[Suzuki and Kodama, 1983]*. The demonstration of such extreme degree of sensitivity of cerebral flow to alterations in PCO2 suggests that "cerebral claudication may even occur" *[Mohr, 1983]*.

Angiography, bolus angiography, digital subtraction angiography and MR angiography have all become popular for demonstratig stenosis or occlusion of the carotid *[Furlan et al., 1983]*. In experienced centers, the combination Doppler to demonstrate high-grade stenosis and the degree of collateral, and MR angiography for anatomy, threaten to replace all invasive angiography in the evaluation of extracranial occlusive disease. Even though the risks are small, angiographic complications in direct injection studies remain a risk to be avoided where possible. However, conventional angiography is still the tool of choice to show ulceration, a component of carotid disease that may still explain many forms of stroke *[Mohr, 1992]*.

CHAPTER 4

CRITERIA OF ADMISSION OF STROKE PATIENTS TO INTENSIVE CARE UNIT

Selection of stroke patients to be admitted to intensive care unit (ICU) is very important because of poor prognosis of most of the cases and high cost expences. The factors that determine admission to ICU for stroke patients is variable from patient to patient and from center to center.

According to Glascow coma score (GCS) table (2), patients with GCS above 7 who need ventilatory support, adjustment of (BP), patients with hyperglycemia or those with electrolyte imbalance can be admitted to ICU. Patients with SAH at the first ten days is a critical condition due to the high possibility of rebleeding and the well documented danger of vasospasm. BP should be monitored around 160/100mmHg; elevation of BP could cause rebleeding and hypertension may agrevates the ischemic effect of vasospasm.

Sedation, calcium channel blockers and cerebral anabolics all should be administered in the ICU.

Table 2: Glascow coma score

Eye opening	
Spontaneous	4
To verbal command	3
To pain stimuli	2
No response	1
Motor response	
Moving all four limbs	6
Localising pain	5
Flexion withdrawal	4
Abnormal flexion	3
Extension	2
No response	1
Verbal response	
Oriented & conversus	5
Confused conversus	4
Inappropriate words	3
Icomperhensible sounds	2
No response	1

Uncontrolled fits secondary to grave stroke, as in major vessel thrombosis, with the additional brain edema and rapid deterioration of consciousness should be managed in the ICU. ICU roles should be followed including continuouns diazepam or barbiturate drip, cerebral dehydrating measures, ventilation and circulatory support.

In some cases of ICH, there is possibility of need to surgical intervention as: if bleeding is cortical, well formed, causing major mid-line shift or deterioration of the neurological deficit. The general and neurological conditions of these patients need stabilization before surgery, this is preferable to be in the ICU. Post-operative ICU admission is mandatory till the condition is stabilized.

CHAPTER 5

MANAGEMENT

Potential strategies for treatment of acute cerebral ischaemia

Acute cerebral ischaemia is a neurological emergency. The management of the stroke patient deserves the same urgency and vigilance as that of the patient who has acutely experienced a traumatic brain injury. A combination of the following therapeutic modalities should be considered which can be summarized as follows:

Table 3: Therapeutic modalities for stroke patient

1- Acute resuscitation of the stroke patient:

a) Maintenance of airway and adequate ventilation.
b) Maintenance of adequate blood volume and BP.
c) Correction of hyperglycemia, hyperthermia and low cardiac output.

2- Reperfusion of ischemic brain:

a) Thrombolytic therapy.
b) Hypervolemic hemodilution.
c) Anticoagulation.

3- Decreasing cerebral metabolic demands:

a) Hypothermia
b) Barbiturates.

4- Inhibition of the degenerative ischemic cascade:

a) Calcium antagonists.
b) Excitatory amino acid antagonists.
c) Free radical scavengers.

[Tranmer et al., 1996].

Appropriate brain resuscitation can prevent secondary injury to the brain and may even prevent progression of the initial ischemic insult. Secondary insults such as hypoxia, hypotension, hypovolemia, decreased cardiac output, hyperthermia and hyperglycemia have been shown to be detrimental to injured brain and can potentially be prevented by routine resuscitative procedures. Maintenance of an adequate airway and proper ventilation is mandatory. Supplementary oxygen, proper head positioning, and frequent suctioning may be all that is necessary to ensure proper blood oxygenation in the "typical stroke patient". However, in the unconscious patient, intubation and mechanical ventilation may be required *[Tranmer et al., 1996]*.

Cerebral ischaemia is extremely sensitive to fluctuations in BP and cardiac output. In ischemic brain tissue, autoregulation fails and CBF varies directly with BP. A decrease in BP aggravates cerebral ischaemia, and elevations in BP increase the CBF to the poorly perfused tissues *[Hillen et al., 2000]*.

It was demonstrated that a significant increases in CBF following induced hypertension. After induced hypertension, neurological status improved, local CBF increased, and infarction size decreased. Although hypertensive therapy can improve CBF in ischemic brain, the risks of this therapy should be realized *[Klungel et al., 1999]*.

Elevation of BP is hazardous in a patient with an unclipped cerebral aneurysm *[Makino et al., 2000]*. Also, the risk of hemorrhage into ishemic brain is a well-known

complication of this treatment and may be particularly hazardous in patients with large areas of ischemic damage.

It have been noted an increase in brain edema leading to rapid deterioration when BP was elevated late in the course of cerebral ischaemia *[Levy et al., 1993]*.

In addition, induced hypertension may be hazardous to elderly patients with cardiac problems. As the brain autoregulates CBF to changes in systemic BP, it also regulates CBF with respect to cadiac output. In ischemic brain, this regulatory process is lost and CBF changes directly with changes in cardiac output. Cardiac output varies directly with volume status and can also be abnormally low in elderly stroke patients with congestive heart failure or cardiac arrhythmias. Thus, in stroke patients, maintaining adequate inravascular volume is important and correcting cardiac abnormalities may prevent further ischemic damage. A central venous line or even a Swan-Ganz catheter may be necessary in patients when fluid status or even cardiac status is a concern *[Tranmer et al., 1992]*.

The temperature of the stroke victims is also critical in the acute phase of ischaemia. Hypothermia of even 2 to 3°C has been shown in the laboratory to be very protective while elevation of temperatue above 37°C aggrevates ischemic brain injury *[Zhang et al., 1993]*. Stroke patients may become dehydrated or develop lung congestion during the early phases of their "expected" stroke therapy, thus, the hypovolemia and elevated temperature may only worsen the already present brain injury *[Corbett et al., 1990]*.

In animal studies, an elevated blood glucose level has been shown to worsen experimental cerebral ischaemia *[Chopp et al., 1988]*. Clinically, patients with ischemic symptoms who also had elevated blood glucose level on admission to a hospital had worse clinical neurological outcomes than those patients without elevated blood glucose values. It is thus recommended that a stroke patient should not receive high-glucose-containing solutions and that the blood glucose level should be maintained as close to normal as possible. Insulin may even play a role if blood sugar levels remain high despite glucose restriction *[Tranmer et al., 1996]*.

Reperfusion of the ischemic brain

Thrombolytic therapy

For ischemic and hemorrhagic stroke, the potential therapeutic role of thrombolytic and defibrinogenating agents has evoked considerable interest *[Brott, 1992]*. Increasing laboratory and clinical experience with thrombolytic agents such as urokinase, streptokinase and recombinant tPA has demonstrated significant and sustained neurological improvement when the thrombolytic treatment has been initiated in the first few hours (Table 4) *[Wang et al., 2000]*.

Early clot lysis was documented for 50% of the stroke patients treated with intra-arterial streptokinase or urokinase following a variety of dosage regimens (Table 5) *[Cruz-Flores et al., 1998]*.

Table 4: Pilot stroke trials demonstrating the safety of rt-PA.

Study	Patients Enrolled (*n*)	Study Design	Therapeutic Window (min)	rt-PA Dose (mg/kg)	Symptomatic Intracranial Hemorrhage (*n*)	Asymptomatic Intracranial Hemorrhage (*n*)	Death at 3 Months (*n*)	Major Neurologic Improvement at 3 Months
Brott et al[18]	74	Open label	≤90	0.35–0.85	0/48	3/71	12/74	24%
				0.95–1.08	3/26			
Haley et al[48]	20	Open label	≤180	0.6	0/8	1/8	2/8	4/8
				0.85	1/6	1/6	3/6	0/6
				0.95	1/6	2/6	1/6	0/6
				Totals	2/20	4/20	6/20	20%
Haley et al[49]	27	Randomized, double-blind	<90	0.85	0/10	0/10	1/10	5/10
				placebo	0/10	0/10	2/10	5/10
			91–≤180	0.85	0/4	0/4	0/4	3/4
				placebo	1/3	0/3	1/3	2/3
				Totals treated:	0/14	0/14	1/14	57%
				Totals placebo:	1/13	0/13	3/13	54%

[Brott et al. 1992].

Table 5: The results of streptokinase trials for the therapy of acute stroke.

Study	Patients Enrolled (*n*)	Study Design	Therapeutic Window (*n*)	Outcome Measures	Intervention	Symptomatic Intracranial Hemorrhage (*n* and %) Odds of AE 95% CI, $P<0.05$	Deaths at 10 Days (*n* and %) Odds of AE 95% CI, $P<0.05$	Death and Disability at Months (*n* and %) Odds of AE 95% CI, $P<0.$
MAST-I	622	Randomized unblinded	≤ 6	Death and modified Rankin scale at 6 months	SK 1.5 MU $n = 157$	10 6	30 19 *1.6 (0.8–3.1)*	97 62
					ASA 300 mg $n = 153$	3 2	15 10 *1.5 (0.9–2.3)*	94 61 *0.9(0.6–1.3)*
					SK + ASA $n = 156$	15 10	53 34 *3.5(1.9–6.5)*	99 63
					neither $n = 156$	1 0.6	20 13	106 68
MAST-E	270	Randomized double-blind	≤6	Death and disability at 6 months	SK 1.5 MU $n = 137$	24 18 *5.82 (2.40–14.11)*	48 35 *2.16 (1.32–3.53)*	61 45 *1.44 (0.99–2.1*
					placebo $n = 133$	4 3	24 18	47 35.3
ASK	340	Randomized double-blind	≤ 4	Death and Barthel Index at 3 months	SK 1.5 MU $n = 106$		46 43.4* *2.65 (1.52–4.61)*	66 62.3† *2.12 (1.26–3.5*
					placebo $n = 122$		27 22	53 43

*Mortality reported at 90 days.
†Death or Barthel Index < 120.
ASK = Australian Streptokinase Trial; MAST-E = Multicenter Acute Stroke Trial, Europe; MAST-I = Multicenter Acute Stroke Trial, Italy; AE = adverse effects of ther. compared with placebo: death and intracranial hemorrhage; SK = streptokinase; MU = million unit.

[Brott et al. 1992].

Table 6: Recanalization following thrombolytic therapy*

Agent	Time	No. treated	No. (%) recanalized	Stroke type
IA UK or SK	<2wk (29≤24h)	43	19 (44)	Vertebrobasilar
IA UK or SK	1-24h (7.6h mean)	20	15 (75)	Carotid
IA UK	50min-12h (4.5h mean)	22	10 (45)	MCA
IA SK	30min-3wk	12	12 (100)	Carotid
IA SK	2h-7days	15	7 (47)	Carotid (9) Vertebrobasilar (6)
IV tPA	≤8h	57	22 (38)	Carotid Vertebrobasilar
Total		**169**	**85 (50)**	

IA = intra-arterial; UK = urokinase; SK = streptokinase; IV = intravenous; tPA = tissue plasminogen activator; MCA = middle cerebral artery.

* includes those studies with pre- and post-treatment angiography.

[Brott, 1992].

Successful recanalization was accomplished in patients with cardiac embolic stroke, patients with atherothrombotic stroke and patients with atheroembolic stroke including patients with vertebrobasilar stroke *[Hacke et al., 1988]*. Large thrombi were less likely to be lysed in patients treated with urokinase reported by Mori et al. (1988). With stroke, some of the thrombi could be older, better organized with more fibrin cross-linking, and so resistant to thrombolysis. Long, large thrombi may be lodged quietly in the distal internal carotid artery disturbed only by arterial pulsation, with minimal surface area exposed to endogenous (or exogenous) thrombolytic substantes *[Brott, 1992]*.

The earlier thrombolytic studies were not performed with clot-specific thrombolytic agents such as streptokinase and urokinase. Improvement in the thrombolytic process has been achieved with serine proteases (included in the endogenous thrombolytic system). Recombinant tPA is not produced in vitro *[Wang et al., 2000]*. It is a relatively clot-specific agent initially used in the treatment of MI and infarction due to intracoronary thrombosis *[Anderson et al., 1998]*. Streptokinase and recombinant tPA appear to be equally effective in the treatment of acute MI. Stroke, especially hemorrhagic stroke, and other bleedings side effects are a major concern of MI patients given fibrinolytic therapy *[Sloan and Gore, 1992]*. It was suggested that the clot-specific recombinant tPA is associated with a higher ICH rate than streptokinase *[Tranmer et al., 1996]*.

The initial work with streptokinase and urokinae in human ischemic stroke was disappointing, and it was thought that the relatively fibrin-specific recombinant tPA would be more effective and be associated with fewer hemorrhagic side effects *[Cruz-Flores et al., 1998]*. Initial animal studies were performed by Zivin and Coworkeres (1988) and it was shown that if the activator was given up to 45 minutes after the onset of stroke there was an improved neurological outcome without increasing hemorrhagic risk. Wang and coworkers, (2000), in an embolic stroke model, provided evidence that recombinant tPA induced clot lysis, reduced infarction size, improved neurological outcome, and reduced mortality.

Beside hemorrhagic risk, there are potential non hemorrhagic complications of thrombolytic therapy as:

Reperfusion injury

Reperfusion injury associated with edema following presumed thrombolytic arterial recanalization has been suggested as the cause of death in some patients *[Brott, 1992]*.

Arterial reocclusion

Arterial reocclusion after successful thrombolysis has not been documented for stroke patients. Recurrent ischaemia (with probably reocclusion) occurs in approximately 15 to30% of patients treated with thrombolytic agents for acute MI *[Ellis et al., 1989]*. Reocclusion is less likely to occur in stroke patients. Many of the occlusions are embolic with the acute thrombus lodged distally in the relatively normal vessel, overlying previously normal endothelium *[Fieschi et al., 1989]*.

Embolism from incidental or therapeutic lysis

Downstream systemic or brain embolism from incidental or therapeutic lysis of large thrombi could complicate thrombolytic treatment for stroke or for MI *[Libman et al., 2000]*.

Other problems

- *Emergency assessment of vascular an*atomy: the time window for effective stroke therapy may be quite small, and older thrombi are more resistant to thrombolysis *[Brott, 1992]*. Thrombolysis-related ICH may be lower with earlier treatment *[Libman et al., 2000]*. Rapid

patient assessment is ideal *[Fieschi et al., 1989]*. Unfortunately, adding cerebral angiography to the necessary CT scan adds a minimum of 30 to 60 minutes before thrombolytic therapy can begin. Eliminating pretreatment angiography has the disadvantage of delivering therapy "in the dark" *[Marler et al., 1997]*.

TCD, MRI angiography and SPECT can provide pre- and post-treatment cerebrovascular anatomic or physiologic information *[Brott, 1992]*. Unfortunately, limitations regarding cost, availability, and the requirement for highly skilled technicians will probably limit development of these techniques. Using emergency brain CT for clues to thrombus localization has been described, but this technique will likely to be limited by low sensitivity and variable reliabiliy *[Tomsick et al., 1990]*.

- *Combination therapy*: The role of platelets in fibrinolysis has been reviewed. Combination of thrombolytic agents with antiplatelet drugs could be useful, particularly as platelet activation may occur in humans following thrombolytic therapy *[Kerins et al., 1989]*.

Hypervolemic hemodilution therapy:

Hypertensive hypervolemic hemodilution is an effective treatment for cerebral ischaemia secondary to cerebral vasospasm *[Kindt et al., 1980]*. Both elevation of BP and colloidal volume expansion augment CBF to ischemic brain, and the clinical outcome of patients with cerebral vasospasm has improved since this therpay has become popular. With the use of artificially induced

hypertension in the treatment of patients with ischemic deficits associated with vasospasm, Kindt and associates became aware that most of the patients were hypovolemic. It was also noticed that once therapy used to increase intravascular volume was instituted, both the amount and the duration of vasopressor therapy could be reduced. Subsequently, these researchers demonstrated that intravascular volume expansion, independent of induced hypertension, was effective in treating the ischaemia secondary to vasospasm. Thus, colloidal volume expansion with or without hypertensive therapy has become a popular and successful method of treating ischemic neurological deficits associated with cerebral vasospasm.

However, randomized multicenter trials have failed to demonstrate a benefit in patients treated with hemodilution *[Troy et al., 1988]*. However, Goslinga and coworkers in 1992, demonstrated a significant reduction in mortality at 3 months and an increase in independence at home in the patient group was treated with hemodilution using albumin and crystalloids.

The mechanism by which colloidal volume expension increases local CBF and decreases infarction volume remains controversial. Wood and Feischer in 1982, coined the term "hypervolemic hemodilution" and have demonstrated that local CBF correlates inversely with both hematocrit and blood viscosity and is directly related to total blood volume. Dextran has also been shown to have antisludging effects by charge-coating the red cells and platelets, thus inhibiting their aggregation *[Tranmer et al., 1996]*. Hetastarch is a synthetic colloid available as a 6% solution in isotonic saline. It has a

high-colloidal osmotic pressure and causes a great plasma volume expension. It has a long elimination half life and its oncotic effects disappear after 24 hours.

Penta starch is a low molecular weight derivative of hetastarch that is available as 10% solution in isotonic saline. It has a higher colloidal osmotic pressure and more effective as volume expander. Its oncotic effects disappear after 12 hours.

Colloidal volume expansion augments cardiac output. Increases in cardiac output during volume expansion are closely followed by increases in local CBF in ischemic brain *[Ohtaki and Tranmer, 1993]*. They also demonstrated that, in normal brain, changes in cardic output did not alter CBF, however, in ischemic brain, CBF changed passively as cardiac output increased and decreased.

The risk of this therapy has been found to be minimal, hemorrhagic complications have not been a problem. Also, cerebral edema of the ischemic brain has generally not been a problem clinically or experiementally. Colloidal volume expansion does play a role in the treatment of acute ischemic stroke, however, the agents to be used, doses to be given and timing of the therapy remain controversial. Central venous pressure monitoring or even the use of Swan-Ganz catheters is suggested to accurately monitor fluid status and critically titrate cardiac function *[Tranmer et al., 1996]*.

Anticoagulation and antithrombotic therapy:

Patients who have already completed a thrombotic event would not benefit from antithrombotic therapy. On

the other hand, patients with a prothrombotic state, such as lupus anticoagulant, ongoing thrombosis formation, or underlying cardiac conditions likely to cause recurrent embolization, would be more logical candidates *[Grotta, 1992]*. In an attempt to evaluate anticoagulation therapy in these subgroups, investigators have recorded the rate of stroke progression and recurrent embolization in patients treated with heparin compared to untreated patients. Duke and co-workers in 1986, found a slight nonsignificant reduction of progression in patients with acute partial thrombotic stroke treated with heparin. Slightly more convicing benefit has been reported in patients with major brain stem infarction. Based on these data, heparin was believed not to be useful for the treatment of acute ischemic stroke *[Tranmer et al., 1996]*.

If heparin therapy is chosen for such patients, it should be under taken with the following caveats: a high-resolution CT scan should be done to exclude hemorrhage, lumber puncture is not necessary to detect hemorrhage if a high resolution CT is negative *[Bienfact et al., 1995]*. Prolongation of the partial thromboplastin time, and the platelet count should be followed daily to detect heparin-induced thrombocytopenia, which may lead to systemic vascular occlusion *[Bruijn and Stam, 1999]*.

The complication rate of anticoagulation in acute ischemic sroke is significant. The incidence of major brain hemorrhage in the anticogulated stroke patients varies widely but is generally reported to be 5 to 15% *[Frey et al., 1999]*. Based on the previously discussed study, early anticoagulation with heparin is believed to be the

appropriate treatment for patients who have suffered a cardioembolic stroke. This therapy should be instituted only after CT has ruled out an ICH or a large cerebral infarction *[Tranmer et al., 1996]*.

Bruijn and Stam in 1999, used subcutaneous low-molecular weight heparin in a therapeutic dose instead of intravenous unfractionated heparin. In patients with leg vein thrombosis or pulmonary embolism. It was showed that low-moleculr-weight heparins are as effective as unfrationated heparin and cause fewer hemorrhagic complications *[The Columbus Investigators, 1997]*. An additional advantage is that low-molecular-weight heparin can be given in fixed doses, only adjusted for body weight, without laboratory monitoring *[Lensing et al., 1995]*. These were no confirmed thromboembotic complications *[Bruijn and Stam, 1999]*. Low-mlecular-weight heparins (heparinoids) have an antithrombotic effect by blocking factor Xa, but have less antithrombin III activity than heparin *[Grotta, 1992]*.

Decreasing cerebral metabolic demands

Cerebral ischaemia is the result of an imbalance between supply and demand of blood flow and its nutrients. If reperfusion of the cerebral tissue can not occur soon enough, then cerebral protection by decreasing the cerebral metabolic demands may help in preservation of brain tissue until reperfusion can occur. Hypothermia and barbiturates have been recognized in the past as agents that do decrease cerebral metabolic demands and have been studied as cerebral protectors *[Tranmer et al., 1996]*.

Hypothermia

The technique of hypothermia was probably the first method of cerebral protection. Over the past 30 years neurosurgeons, cardiovascular surgeons and anesthesiologists have used hypothermia to protect the brain during periods in which the cerebral circulation had to be greatly reduced or eliminated to permit proper surgical access *[Kramer et al., 1968]*. It has been thought that hypothermia decreases the cerebral metabolic rate. It is demonstrated that cerebral oxygen metabolism decreased in a linear fashion during temperature reduction from37 to 22°C. At 22°C the local CBF and metabolic rates were reduced to about 25% of normal *[Tranmer et al., 1996]*. They also demonstrated that the optimal brain protection was produced at temperatures between 27° and 30°C. However, the clinical usefulness of profound hypothermia has been limited by the adverse side effects associated with the severity and duration of hypothermia *[Zhang et al., 1993]*. Cardic arrhythmias and cardiac arrests have been encountered during neurosurgical operations especially if the temperature was allowed to drop near the threshold for cardiac arrhytmias (27°C). Pulmonary complications such as pneumonia and neurogenic pulmonary edema have also been attributed to hypothermia.

Ridenour and associates in 1992, demonstrated that mild hypothermia reduced infarction size during focal ischaemia. The mechanism by which hypothermia is protective may not be as simple as saying it decreases the cerebral metabolic rate. Busto and associates in 1989, produced hypothermia in a rat stroke model and found that

the release of glutamate and dopamine was dramatically reduced during hypothermic ischaemia. For the time being, maintenance of euthermia and certainly reduction of hyperthermia in the patient with ischemic stroke should be done to reduce progression of the ischemic insult *[Tranmer et al., 1996]*.

Barbiturates

Barbiturates have been reported to provide effective cerebral protection if given before or soon after the onset of cerebral ischaemia in animal studies *[Smith et al., 1974]*. Cerebral protection using barbiturates has also been shown to be of clinical benefit. Hypothermia may have accounted for some of the brain protection that was attribued to barbiturates in these older studies *[Tranmer et al., 1996]*.

Propofol

Propofol is a relatively new nonbarbiturate intravenous anesthetic agent characterized by rapid induction and awakening from anesthesia. Propofol produces dose-related decrease in both CBF and $CMRO_2$.

Propofol distributes evenly throughout the CNS and elicits generalized reduction of CN activity in the rat *[Cavazzuti et al., 1991]*. Likewise, in humans, PET studies demonstrated a global reductioin in CNS metabolism with propofol *[Alkire et al., 1995]*. This reduction in metabolic activity is similar in terms of its homogeneity to that caused by barbiturates.

Propofol is a potent cerebral vasoconstrictor, as a result it decreases ICP. Unfortunately, this beneficial effect on ICP may be countered by a major and sometimes dangerous decrease in MABP secondary to its direct myocardial depressant effect, resulting in a decrease in CPP *[Pinaud et al., 1990]*.

Preadministration of propofol was found to reduce damage from neuronal transmission and to attenuate changes in calcium, potassium and sodium during hyperthermic anoxia (39°C) *[Cheng et al., 1997]*. In rats subjected to incomplete cerebral ischaemia, infusion of propofol in doses that produced EEG burst suppression significantly improved neurologic outcome and brain histopathology. Early recovery of EEG correlated with improved neurologic recovery *[Kochs et al., 1992]*. The depression of $CMRO_2$ by propofol was greater than that by halothane, yet neurologic outcomes did not differ *[Cheng et al., 1997]*.

Propofol, at clinically relevant concentrations, enhances the inhibitory gamma-aminobutyric acid (GABA) receptor-mediated response in mammalian central neurons *[Hara et al., 1994]*. Propofol directly activates the GABA receptor and potentiates the action of GABA.

Ketamine

Ketamine is an intravenous anesthetic agent. Like barbiturates, ketamine induces anesthesia quickly, however, unlike the barbiturate, ketamine also has analgesic properties.

Concern regarding ketamine's effect on CBF, $CMRO_2$ and ICP has limited the use of this agent in neuroanesthetic practice. Kochs et al. in 1991 demonstrated that in humans ketamine caused an increase in EEG theta activity and CBF velocity as measured by TCD.

Increase in CBF with ketamine may lead to undesirable increases in ICP. However, it did not raise ICP in patients with intracranial tumors or aneurysms when thiopental was administered first *[Mayberg et al., 1995]*. Rats given katamine after head injury demonstrated improved neurologic outcome *[Chang et al., 1997]*.

Similarly, memory retention was improved in ketamine-treated rats. Higher doses of ketamine (upto 60mg/kg) did provide protection, suggeting a dose-related effect, however, the dose necessary for neuroprotection in humans is not clear *[Church et al., 1988]*.

Inhibition of the degradative ischemic cascade

Calcium antagonism

Studies in experimental cerebral ischaemia have demonstrated that calcium influx into cells and liberation of intracellular stores of calcium activates proteases and phospholipases that produce cytotoxic free radicals and leukotrienes, resulting in cell death *[Kaplan et al., 1990]*. The critical rise in intracellualr free calcium concentration during ischaemia occurs through voltage-dependent calcium channels, receptor-operated calcium channels, and release from endoplasmic reticulum *[Meyer, 1989]*.

Calcium antagonists may beneficially modulae ischemic brain damage either by increasing blood flow through the vasodilation of cerebral vessels or by protceting the neurons by blocking calcium entry into the cell during ischaemia or by antagonizing the intracellular action of calcium *[Grotta, 1992]*. Calcium channel blockers prevent calcium influx through one of the three known voltage-operated channels (L type) *[Tranmer et al., 1996]*.

Nimodipine has been demonstrated to protect against the ischemic effect of vasospasm and is commonly used in patients with SAH *[Grotta, 1992]*. Despite encouraging results using nimodipine in animal stroke models, results of clinical stroke trials have been mixed *[Gelmers et al., 1988]*. Their study showed that nimodipine, 30mg four times a day, given within 24 hours of the stroke significantly reduced morbidity. However, more studies have not shown any positive effects of nimodipine *[Bogousslavsky et al., 1990; Martinz-Vila et al., 1990]*. It was suggested that nimodipine may be effective in patients with moderate deficits who are treaed within 12 hours of the ischemic event. Nimodipine was not associated with significant hypotension or other serious side effects. However, Nicardipine, another voltage dependent calcium channel blocker hypotension and tachycardia were noted *[Grotta, 1992]*.

Excitatory amino acid antagonists

The blockade of the voltage-sensitive calcium channel alone during cerebral ischaemia may not be sufficient to dramatically affect the rapid rise in inracellular calcium

[Albers et al., 1989]. Activation of receptor-operated calcium channels by excitatory amino acids, especially glutamate, appears to be an important inducer of intracellular calcium, and it is hypothesized that blockade of these channels may protect the ischemic neuron *[Grotta, 1992]*.

The receptor-operated calcium channels include N-methyl-D-aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazole propenate, and metabotropic subtypes *[Seijo and Begstsson, 1989]*. The NMDA channels can be blocked by both noncompetitive (MK 801) and competitive antagonists. The agent MK 801 and dextromethorphan significantly decrease neuronal damage in experimental ischaemia *[Tranmer et al., 1996]*. Although these antagonists have been shown to be experimentally beneficial during moderate ischaemia, reproducible protection has not been reported in models of severe ischaemia *[Buchan et al., 1991]*. The protective effect of MK 801 may be due to its hypothermic effect on the animals as opposed to a direct cytoprotective effect *[Corbett et al., 1990]*. The α-amino-3-hydroxyl-5-methyl-4-isoxazole propenate antagonist 2,3-dihydroxyl-6-nitro-7-sulfamoyl-benzoquinoxaline has been shown to be a powerful cerebral protector during severe forebrain ischaemia and during transient focal ischaemia *[Tranmer et al., 1996]*. Clinical trial is necessary to study these agents for both safety and efficacy in humans.

Free radical scavengers

Free radical generation during ischaemia and reperfusion is believed to be the final common pathway for neuronal damage during ischemic stroke. Free radical scavengers such as tirilazad and super oxide dismutase have been shown to be protective in animal models *[Grotta, 1992]*. The efficacy of tirilazad in patients with SAH has been compelted and demonstrated a 44% decrease in morbidity secondary to vasospasm. A clinical stroke trial is also underway to evaluate the efficacy of tirilazad in ischemic stroke *[Tranmer et al., 1996]*. Mannitol is a hydroxyl free radical scavenger and is routinely given by neurosurgeons intraoperatively during "planned" vessel occlusion during aneurysm surgery *[Imaizumi et al., 1989]*.

Other therapy

Steroids

There is no evidence supporting the routine use of glucocorticoids for acute cerebral infarct *[DeReuck et al., 1988]*. Theoretically, steroids have some free radical scavenging effect and may reduce vasogenic edema, but this is usually not a major contributor to cerebral edema after acute infarction *[Grotta, 1992]*.

One condition for which steroids are probably of value is cerebral arteritis. Steroids have been used as the first line of treatment for both systemic rheumatic diseases affecting the brain and for isolated CNS angiitis *[Paal et al., 1989]*. Therapy should be continued until disease activity disappears either by serologic markers or by arteriogrpahy, and then slowly withdrawn *[Grotta, 1992]*.

Antidepressants

Depression has been recognized in 30 to 50% of patients during the first year after stroke but may not occur until the patient leaves the hospital and rehabilitation setting. Such depression is often shows a gratifying response to tricyclic antidepressant therapy.

Physical, occupational and speech therapy physical, occupational and speech therapy are of value although studies have had conflicting results *[Wentz et al., 1986]*. One anecdotal report emphasizes that frequent and prolonged therapy can result in improved language function *[Wender, 1989]*.

Increased intracranial pressure

When uncontrolled intracerebral pressure ICP is associated with decreasing level of consciouness or other signs of herniation, the patient should be carefully intubated and hyperventilated remembering that excessive coughing or straining associated with intubation causes a dramatic increase in ICP *[Grotta, 1992]*.

Morphine sulfate intravenously can allay agitation in patients requiring intubation who are still conscious and is a useful adjunct in controlling ICP. Muscular paralysis with metacurine may be necessary and is a better choice than pancuronium, which is a sympathomimetic and may cause hypertension and tachycardia *[Tranmer et al., 1996]*. The head should be elevated 30 degrees in all patients with increased ICP *[Grotta, 1992]*.

It may be necessary to lower MABP to prevent renal and cardiac injury. However, cerebral perfusion pressure

(CPP) must be maintained above 50 mmHg to insure adequate CBF. In controlled dangerously increased MABP, the best approach is first, make every effort to lower ICP *[Bullock et al., 1996]*.

Though nitroprusside has been used most freqeuntly, parenteral beta blockers prevent associated sympathetic over activity. Diuretics are often given, but it is essential to avoid volume depletion or hemoconcentration, and careful volume expansion with isotonic fluid may be indicated to maintain optimal cardiac output and tissue perfusion *[Rhee et al., 2000]*.

Osmotic therapy with mannitol should be given acutely for uncontrolled increased ICP, and can be used repetitively to help control ICP on a longer-term basis *[Angle et al., 1998]*.

Vasospasm

The most common cause of morbidity after aneurysmal SAH is cerebral ischaemia resulting from arterial spasm *[Indredavik et al., 1998]*. Nimodipine reduced mortality and bad outcome due to vasospasm, and this drug is approved for noncomatose patients *[Tranmer et al., 1996]*.

Adjunctive therapy for vasospam, namely volume expansion can be carried out once the aneurysm is successfully clipped and raising perfusion pressure by vasopressors if necessary *[Indredavik et al., 1997]*. Appropriate monitoring of intravascular volume, cardiac output and ICP are important if these treatments are instituted *[Yamaguchi et al., 1997]*.

CHAPTER 6

COMPLICATIONS AND MANAGEMENT

Cardiovascular and pulmonary functions

Cardiovasclar and pulmonary complications associated with strokes are due to preexisting diseases, which can be aggrevated by stroke, stroke-induced cardiac arrhythmias and ECG abnormalities, neurogenic pulmonary edema (NPE) and hypertension and the potential problems associated with its aggressive therapy. Berg and Intrator, (1996), with preexisting cardiovascular and pulmonary diseases, strokes may worsen the underlying condition due to either neurologic deficits of secondary metabolic derangement *[Jorgensen et al., 1997]*. Table (7) summarize medical and neurologic complications of stroke.

Table 7: Medical and neurologic complications of stroke

Cardiovascular and pulmonary fuctions	Cardiac arrhythmias, candiac output , BP stabilization, hypertension, congestive failure. Chronic obstructive pulmonary disease, pulmonary embolism, atelectasis, neurogenic pumonary edema, pneumonia, intubation, tracheostomy
Nutritional and metabolic status	Intake and output, body weight, electrolytes and mineral metabolism. Salt and water metabolism: syndrome of inappropriate antidiuretic hormone secretion, CNS salt losing, a salt retention
Excretory fucnion	Bladder incontinence, "spastic bladder", hypotonicity/retention. Bowel: incontinence, constipation.
Bed rest and immobility	Skin care: decubiti and sores contracture Venous thrombosis and pulmonary emboli Atelectasis
Psychiatric disorders	Depression Confusional states: organic brain syndrome and sundowning
Neurologic complications	Seizures (general, partial) Increased intracranial pressure Coma/stupor Cognitive defects and dementia

[Yatsu et al., 1992].

It has been recognized for years that cerebral vascular events, such as SAH, acute thromboembolic stroke and cerebral hemorrhage have been associated with abnormalities on the ECG. ECG changes were QT prolongation (up to 45%), ST segment depression or T-wave inversion (35-50%) and U waves (up to 28%) *[Yatsu et al., 1992]*.

Patient with severe coronary artery disease subjected to sympathetic nervous stimulation due to an intracerebral event could clearly cause cardiac changes such as ischaemia or arrhythmias. The discharge of catecholaminergic neuro-transmitters into the systemic circulation in association with cerebral infarction, SAH and increased ICP, plus increased vagal traffic to the heart, provokes both hypertension and cardiac muscle damage *[Norris, 1983]*.

Treatment modalities for these cardiac changes include beta-blockers to inhibit the catecholaminergic output, lidocaine for dysrythmias, and atropine for vagotonia *[Yatsu et al., 1992]*.

With pulmonary diseases such as chronic obstructive pulmonary disease (COPD), weakness of muscles of respiration due to hemiparesis, impairment of respiration due to brain stem lesions, and inadequate cough and gag leading to aspiration will embarrass and decompensate borderline pulmonary function. In addition, immobility of extremities due to paralysis with attendant stasis of blood and thrombosis can lead to multiple pulmonary emboli. In addition, atelectasis secondary to immobility can lead to

hemoglobin and tissue desaturation and thus lead to further hypoxic insult *[Touho, 1989]*.

In patients with mildly impaired gag or swallowing frequent suctioning and avoiding the supine position are indicated but if gag and swallowing are seriously affeted, either intubation or tracheostomy should be instituted to avoid the dangers of aspiration *[Yatsu et al., 1992]*.

NPE occurs in association with dramatic insults to the CNS, such as massive SAH, seizures or head trauma *[Drislane and Samuels, 1988]*. Although NPE occur from congestive heart failure resulting from massive and sustained hypertension secondary to catecholaminergic release, the most common mechanism in causing NPE is transudation of serum into lung alveoli *[Touho, 1989]*. The primary disorder with NPE is increased extravascular lung water caused by high permeability of water leading to pulmonary edema *[Theodore and Robin, 1975]*. Although α-adrenergic blockade, such as the use of phenoxybenzamine, has been advocated, institution of positive end-expiratory pressure suffices in clearing the patient of NPE *[Yatsu et al., 1992]*.

Hypertension in acute stroke should not be treated unless to a modest degree of 10 to 15% reduction or if the patient has evidence of hypertensive encephalopathy *[Brott and Reed, 1989]*. One of the major reasons for not reducing BP is to maintain necessary perfusion pressure of the cerebral circulation to ensure adequate tissue access to obligatory nutrients of oxygen and glucose *[Hillen et al., 2000]*.

The classic observation on CBF in hypertensives showed that these individuals lose homeostatic control when the MABP is reduced to below approximately 125mmHg *[Gueyffier et al., 1997]*. Hayashi in 1988, investigated stroke patients with increased ICP using intraventricular recording devices, and found that hypotensive agents, such as calcium channel blockers, could produce a profound increase in ICP due to vasodilatation, while only a trivial reduction in systemic arterial pressure occurred. These studies confirm the long-feared complication of hypotensive therapy in patients with strokes by compromising the perfusion pressure.

Nutritional and metabolic status

Nutritional up keep/balance and metabolic homeostasis are constantly threatened in stroke patients who may suffer inadequate intake of food and fluids because of sensorial depression, altered thrist mechanisms or dysphagia *[Indredavik et al., 1999]*. For patients at risk of aspiration, either temporary nasogastric tube or percutaneous gastrostomy is indicated to ensure adequate nutrition and fluids. In some patients with severe dysphagia and sensorial depresson in whom aspiration is a serious concern, early tracheostomy is justified to avert pneumonia *[Berg and Intrator, 1996]*. In patients who can handle secretions, but only marginally, the semi-flower's position with the head down and slightly turned with encourage pulmonary toilet to occur by gravity and minimize aspiration, particularly in conjunction with self or aid-administered suctioning *[Jorgensen et al., 1995]*.

Since most stroke patients will not have drunk fluids because of their disability, care should be taken to maximize their fluid balance with regular body weights and checks on intake and output. During hot weather when insensible fluid loss is greater, compensation for this loss must be calculated *[Yamaguchi et al., 1997]*.

For severe strokes, such as massive SAH, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may supervene. The serum sodium begins to fall with evidence of mismatch between serum and urine osmolality and free water is retained in the face, paradoxically of hemodilution. SIADH can be treated with fluid restriction by only compensating for insensible water loss. For severe hyponatremia below 115mEq/L, coupled with evidence of sodium depletion and of sodium loss, infusion of sodium coupled with diuresis is indicated *[Indredavik et al., 1999]*.

Excretory functions

Careful attention to bladder and bowel functions is a normal complement to concerns over hydration, nutrition and metabolic balance, especially in patients whose motor, sensory or mental disabilities do not allow them to communicate their needs for normal excretion. Stroke victims are frequently incontinent of both urine and faeces due to loss of voluntary sphincter control or an inability to respond to sensations warning of either full rectum or bladder *[Kendall and karafin, 1974]*. With brain stem and spinal cord strokes, both efferent and afferent pathways

from bladder and rectum can be impaired, leading to either retention or incontinence *[Yatsu et al., 1992]*.

For urinary retention, catheterization should be the last resort because of the hazards of urinary tract infections. For men, condom catheters can be used for overflow or autonomous bladders, but catheterization, either intermittent or constant indwelling, may be required to avert the potential dangers of hydroureters and hydronephrosis from urinary retention. For women, the problem of incontinence is complicated by the more ready occurrence of skin maceration from incontinence, which justifies catheterization until continence is restored *[Jorgensen et al., 1999]*.

Faecal incontinence occurs for both spinal cord and brain lesions, and the use of diapers with frequent changes can minimize skin maceration. Constipation with fecal impaction can be a serious problem which is better treated by prevention with the use of enemas, rectal examinations, disempactions and diet supplements with fiber*[Yatsu et al., 1992]*.

Psychiatric and psychological disorders

Psychiatric and behavioural complications are common with strokes and are the result both of the patient's reaction to disabling neurologic deficits and of brain damage affecting brain areas provoking behavioral changes *[Benson, 1973]*. In addition, a variety of psychiatric and psychological disorders can occur resulting from neurotransmitter alterations or "chemial imbalances" due to damage to critical areas of brain. These disorders

include not only depression, but mania, agitation, violence and range, and emotional lability *[Robinson et al., 1990]*.

Moderate to severe depression is seen in a large percentage of stroke victims and yet many times goes undiagnosed and untreated *[Yatsu et al., 1992]*.

Use of tricyclic antidepressants have been shown to be very effective in treating post stroke depression. Lipsey et al. in 1984, demonstrated that the use of nortriptyline is effective in treating depression and is well tolerated by patients over extended periods of time. It is recommended to avoid the sedative, anticholenergic or orthostatic side effects, that the patients are started on low doses of the tricylic antidepressants once at night and slowly increased over a 2 to 3 week period of time *[Yatsu et al., 1992]*.

Treatment of other psychiatric disturbances such as agitation, particularly "sundowning" at night may be treated with the major tranquilizers, such as haloperidol or thioridazine *[Brown et al., 1999]*.

Neurologic disorders

Major complications resulting from strokes, particularly ischemic strokes and ICH, include seizures, increased ICP, and significant cognitive impairment *[Xerri et al., 1998]*. Seizures, which occur most commonly with embolic strokes and ICH, must be controlled with anticonvulsants *[Kieburtz, 1990]*. Increased ICP which can only be accurately determined with dural or intraventricular monitoring, should be controlled by hyperventilation and osmotic diuresis to avert potentially lethal herniation syndromes *[Yatsu et al., 1992]*.

Nelles, et al. in 1999, concluded that passive movements in hemiplegic stroke patients before clinical recovery elicited some of the brain activation patterns found in other studies of stroke patients during active movements after substantial recovery had occurred. This analogy between activation patterns of passive and active movements highlights the contribution of afferent synaptic activity for central motor control. Their findings further indicate that reorganization of sensory and motor systems occurs early after stroke. These early changes of cerebral activation may be critical for return of voluntary motor control. Such study may also be helpful in examining the efficacy of rehabilitative interventions targeting restoration of motor function after stroke.

CHAPTER 7

OUTCOME

The most predictive variables of ICU mortality are coma, cardiopulmonary resuscitation, and shock. Coma of greaer than 48 hours duration resulted in a 77% mortality compared with an 11% mortality rate without coma *[Snyder and Colantonio, 1994]*.

Coma or unconsciousness, present in about one-third of all stroke cases, is found twice as often in hemorrhagic as in ischemic strokes. Moreover, the presence of coma increases the risk of fatality by a factor of three to seven, depending on the category of stroke. In all types of stroke combined, the fatality rate of comatose patients in 65%, whereas only 11% of non comatose patients die in the hospital. However, for the comatose cases of intraparenchymal hemorrhage, the fatality rate reaches 84% as compared to only 27% of conscious intra-parenchymal hemorrhage patients *[Koziol and Hacke, 1990]*.

The high incidence and prevalence of stroke as well as the great variation in clinical outcome have led to an interest in identifying accurate predictors of outcome *[Johnston et al., 2000]*. The ability to accurately determine prognosis and predict outcome, both in the initial evaluation of a patient and in subsequent daily assesments as a reflection of the response to treatment, would greatly improve medical practice in ICU. Quantitative risk assessment not only would enhance clinical paractice, but

would contribute to evaluation of quality of patient care, facilitate analysis of the overall performance of the ICU compared with other units or national standards *[watts and Knaus, 1994]*.

Effort should be made to identify key predictive variable and properly weight and integrate them in order to objectively and accurately predict a patient's outcome to reduce uncertainty for the ICU. Knowing expected outcome may also allow improved selection of patients anticipated to respond to therapy.

The great variability of outcome seen in stroke patients has led Johnston and his co-workers in 2000 to be interesting in identifying predictors of outcome. They found a strong multivariable relationship between the 7 variables {6 clinical: age, initial national institutes of Health stroke Scale (NIHSS), small vessel stroke, history of stroke, history of diabetes, prestroke disability and one imaging which is the infarct volume} and excellent outcome (full or nearly full recovery) and the 7 variables and very poor outcome at 3 months after ischemic stroke. Their analysis suggests that future attempts to predict stroke outcome using acute clinical and acute imaging predictor variables would be valuable.

However, in 1999, Tarkowski and his colleagues suggested that the clinical outcome of the disease is not only dependent on the extent of the brain lesion but also on its localization.

In 2000, Papathanassoglou and his co-workers assumed that ICU mortality is more likely to be attributable

to the development of progressive organ system dysfucntion, typically involving multiple systems simultaneously, regardless of the use of aggressive organ support. This clinical entity, termed "multiple organ dysfunction syndrome (MODS), commonly develops secondary to a generalized inflammatory response by the host, a syndrome termed "systemic inflammatory response syndrome (SIRS)". SIRS and MODS are prevalent clinical responses in the critically ill, and constitute a common cause of ICU morbidity and mortality, particularly when complicated by infection (sepsis). Sepsis is the most common cause of death in ICUs *[Barriere and Lowry, 1995]*.

MODS is often irreversible with mortality ranging from 60% to 90% in cases in which dysfucntion involves three or more organs for $\geq$7days *[Marshall et al., 1995]*. To date, there is neither an effective treatment for MODS nor an effective means for preventing its onset *[Papathanassoglou et al., 2000]*. Undoubtedly, understanding the pathophysiologic mechanisms underlying the development of SIRS and MODS should provide important directions for development of successful treatments for these fatal syndromes *[Barriere and Lowry, 1995]*.

Infections, specially that involving lipopolysaccharide (LPS or endotoxin), a component of the gram-negative bacterial cell wall, has long been considered to be a primary trigger for the initiation of SIRS and MODS *[Darville et al., 1993]*. However, evidence also suggests that the massive inflammatory reaction, the final common pathway underlying a multitude of primary insults to the

host that can precipitate SIRS and MODS, is independent of the presence of infection *[Papathanassoglou et al., 2000]*. The generalized inflammatory response is characterized by activation of the central and peripheral nervous systems, release of numerous hormones and production of cytokines. Cytokines, and to a lesser extent reactive oxygen species are the best identified candidates thus far for mediating the development of SIRS/MODS *[Bone, 1996]*.

A relevant downstream effect of cytokines is apoptosis, or programmed cell death (PCD). Apoptosis is an active, gene-directed cellular self-destruction that may occur under physiologic or pathologic conditions. All of the known mediators of SIRS/MODS have the potential to enhance apoptosis in organ tissues and endothelial cells *[Darzynkiewicz et al., 1997]*.

In 1999, Tarkowski and his co-workers has shown a significant decrease of sFas/Apo-1 and sbcl-2, 2 proteins that suppress apoptosis, in the cerebro-spinal fluid (CSF) of patients with acute stroke. In addition, the CSF levels of sFas/Apo-1 were negatively correlated with the degree of neurological deficit and with the volume of brain infarct 3 weeks and 3 months, respectively,after the onset of the disease. Thus, the decreased levels of molecules inhibiting apoptosis observed in their study could be associated with a poorer prognosis. In 1995, Matsuyama et al., observed an increased expression of Fas/Apo-1 in the brain tissue after an ischemic lesion, resulting in incnreaed apoptosis that lead to aggrevated tissue damage during stroke. So, control

of factors regulating apoptosis may lead to decreased delayed brain damage in stroke.

In a study done by Muir et al. in 1999, a single measurement of C-reactive protein (CRP) within 72 hours of symptom onset in ischemic stroke patients was an independent predictor of survival in this study. The excess mortality resulted from cardiovascular disease, with stroke and MI being the most common certified causes of death *[Thompson et al., 1995]*. Previously it is found that the peak CRP level (which occurs at 48 hours or later in MI patients) to be the most valuable outcome predictor *[Liuzzo et al., 1994]*.

In experimental acute stroke, the release of inflammatory mediators (e.g. interleukin-1, interleukin-6, tumor necrosis factor α) in direct response to brain injury occurs within 2 hours of onset of focal ischaemia, and anti-inflammatory therapies are neuroprotective *[Jiang et al., 1995]*.

Beamer and colleagues in 1995 found significantly elevated interleukin 6 in patients after stroke in whom inter-current infection had been excluded. Elevated interleukin 6 and CRP concentrations were present in patients with large established infarcts onCT but not in those with lacunar stroke *[Muir et al., 1999]*. Despite of this later observations, the presence of secondary complications of stroke at the time of sampling; infection, underlying malignancy, or deep vein thrombosis may all cause elevation of CRP and other inflammatory mediators

[Liuzzo et al., 1994]. However, CRP concentration predicted future mortality independently of stroke severity.

The pathophysiological mechanisms responsible for damage of brain mirco-vasculature and parenchyma before, during, and after resuscitation are multiple *[Negovsky, 1988]*. The ability of tissue to survive anoxic no-flow states is drastically reduced in normothermia compared with hypothermia *[Sterz et al., 1996]*. Alterations in body temperature can profoundly affect the mortality from ischemic stroke in laboratory animal models, in which treatment with mild hypothermia (30°C to 34°C) for 3 to 4 hours has been shown to reduce the size of cerebral infarction *[Mann et al., 1999]*. Mild resuscitative hypothermia in patients is feasible and safe. A clinical multicenter trial might prove that mild hypothermia is a useful method of cerebral resuscitation after global ischemic states *[Zeiner et al., 2000]*. Accordingly, hypothermia has been suggested as a mean of neuroprotection in focal cerebral ischaemia.

An association between admission body temperature and stroke mortality was noted independent of clinical variables of stroke severity. Hyperthermia was associated with an increase in one year mortality while hypothermia was associated with a reduction in-hospital mortality *[Wang et al., 2000]*.

Eighty percent of patients with a diagnosis of acute stroke are hypertensive on admission to hospital *[Oppenheimer and Hachinski, 1992]*. Although the elevated BP levels spontaneously decline over the subsequent 7 to

10 days, 30% of patients still may be classified as hypertensive (BP>160/95mmHg) at long-term follow up *[Harper et al., 1994]*. These BP changes appear to be the result of the stroke per se and not of hospital admission as demonstrated by case-control studies *[Britton et al., 1986]*.

Early antihypertensive therapy may improve outcome in subjects in whom there is coexistent cerebral edema, and the introduction of thrombolysis as an acute therapy may have an implication on the management of BP *[Chamorro et al., 1998]*.

The underlying pathophysiological mechanisms for the acute increase in BP levels after both cerebral infarction and hemorrhage are unknown but could be related to an increase in sympathetic nervous system activity, as evidenced by raised plasma catecholamine and corticosteroid levels and damage to the autonomic nervous system, in particular the baroreceptor reflex arc *[Feibel et al., 1981]*.

In 2000 Dawson et al., found that the introduction of an agent that leads to a gradual reduction in BP, improves BP variability and does not negatively affect CBF. For example, a centrally acting agent or an angiotensin-converting enzyme inhibitor, may have a positive role to play in improving prognosis after stroke, even if confind to certain stroke subgroups.

In 2000, Keller and his co-workers found that monitoring of CBF could be of clinical value as a prognostic tool for outcome in patients with acute hemispheric infarction.

In an attempt to improve outcome in patients with traumatic head injury, renewed emphasis has been placed on CPP *[Bullock et al., 1996]*. Therapy directed at improving CPP may be more important than that aimed at elevated ICP.

Currently there is controversy regarding ICP as opposed to CPP management. The trend has been toward a greater emphasis on CPP, according to the concept that relative increase in cerebral perfusion is more important than any potential increase in ICP *[Rosner, 1995]*. However, in 2000 Juul et al., data strongly indicate that elevated ICP is the major risk factor for neurological dterioration in severely head injured patients, implying a potentially worse neurological outcome. They concluded that, treatment protocols for the management of severe head injury should emphasize the immediate reduction of raised ICP to less than 20mmHg if possible. A CPP greater than 60mmHg appears to have little influence on the outcome of patients with severe head injury.

It remains highly speculative whether any of the new therapeutic modalities will benifit stroke patients, or not *[Biller and Love, 1991]*. The experience of the 1970's demonstrated that stroke ICUs did not sigificantly reduce morbidity and mortality *[Millikan, 1979]*.

In 1997, Marik, reported that fifty seven percent of the patients treated in their ICU after suffering a severe stroke were discharged alive from hospital. However, all of these patients were severely disabled and required special care in a chronic care facility. These results support

the data from the early 70's that stroke intensive care units have very little impact on patients following a stroke *[Millikan, 1979]*.

The management of patients following a cerebro-vascular accident largely involves good nursing care and a well-organized multidisciplinary rehabilitation program *[Dennis and Langhorne, 1994]*. Acute medical interventions have not been established to improve outcome, and in fact may be harmful in some circumstances *[Calhoun and Oparil, 1990]*. Although intubation and hyperventilation are routine, though heroic, measures in patients after severe stroke, their efficacy in reducing mortality and improving functional recovery has never been established. In fact, hyperventilationwith induced hypocarbia, may reduce perfusion to the penumbral brain regions and increase infarct size. Furthermore, isovolemic hemodilution, corticosteroids osmotic diuretics, barbiturates and acute thrombolysis have not been demonstrated to improve the outcome of patients who have suffered a cerebrovascular accident *[Hacke et al., 1995]*. Surgical intervention is only indicated in patients with large cerebellar infarcts or bleeds that compress the brain stem and in patients with an acute obstructive hydrocephalus *[Adams et al., 1994]*. The emergent reduction of BP in a hypertensive patient may be hazardous and increase the size of the stroke *[Gifford, 1991]*. Antihypertensive treatment is therefore not recommended for patients with stroke except in cases of extreme BP elevation and in these cases treatment with oral antihypertensives usually suffices *[Kelly and Luce, 1993]*.

The report from the stroke council of the American Heart Association recommends that "protecting the airway and providing ventilatory assistance are critical components of resuscitation in patients with stroke who have impaired consciouness" *[Adams et al., 1994]*. Marik in 1997, disagreed with this therapeutic strategy for a number of reasons; patients with an absent gag reflex on admission to hospital will almost always die from their stroke and intubation and mechanical ventilation may only prolong the dying process and increase the risk of developing further complications. There is, considerable evidence that endotracheal intubation and mechanical ventilation increases the incidence of pneumonia, acute bronchitis, sinusitis, atelectasis and many other complications *[Rouby et al., 1994]*. So, Marik in 1997, recommended that endotracheal intubation should only be performed in patients with reversible respiratory failure. In 1994, Burtin and his colleagues, found that the severity of neurological impairment as reflected by the Glasgow coma score was the best predictor of stroke patients following admission to the ICU. Neither the location or type of stroke, nor the patients co-morbidities were significant prognostic factors.

The function of an ICU is to provide temporary physiological support for patients with potentially reversible organ failure *[Kotila et al., 1998]*. When poorly selected patients are admitted to the ICU, the inappropriate use of technology may not save lives, nor improve the quality of life, but rather transform dying into a prolonged, and miserable process *[Marik, 1997]*. If aggressive treatment in an ICU delays or prolongs dying and causes

discomfort, the procedure should be considered harmful to the patient and should not be offered *[Bleck et al., 1993]*. Marik in 1997, believed that most patients suffering a cerebrovascular accident are best cared for in specialized stroke units. This is in agree with the conclusion done by Jorgensen and his co-workers in 2000, that completely unselected patients with stroke all appear to benifit from treatment and rehabilitation in a dedicated stroke unit regardless of their age, sex, co-morbidity and stroke severity. Furthermore, patients suffering a cerebrovascular accident should only be admitted to an ICU if they develop an acutely reversible medical complication and have a good prognosis for a functional recovery *[Hackett et al., 2000]*.

SUMMARY

SUMMARY

Stroke is the commonset cause of death after heart disease and cancer particularly among the elderly. In spite of achievment of medical and surgical therapies of stroke, prevention will be the most effective strategy in reducing thė damage from impending stroke. Prevention will be facilitated by understanding predisposing host and environmental factors.

Hypertension is the most powerful risk factor of stroke. Therefore, there is no doubt that control of hypertension is particularly important for the prevention of sroke. Stroke is more likely to be the initial manifestation of cardiovasclar disease among hypertensives. Other cardiac disorder associated with increased risk of ischemic stroke are AF, acute MI and mitral valve disease. Low serum cholesterol level was found to increase the incidence of ICH while there was direct relationship between high levels of total serum cholesterol and ischemic stroke, particularly in hypertensives. Also, D.M. was recognized as an important risk factor for the development of stroke. Meanwhile proteinuria was found to be an independent risk factor for stroke in patients with NIDDM.

Other risk factors were demonstrated as high normal hematocrit level, fibrinogen and high leptin level. An inverse relationship was found between electrolyte intake, as calcium and potassium, and risk of ischemic stroke. Recent heavy alcohol consumption and cigarette smoking were linked to stroke. Regarding medication oral

contraceptives were found to increase risk of stroke while antiplatelet drugs and anticoagulants are beneficial in the prevention of stroke.

The development of a focal neurologic deficit is designated stroke, the cause of which is a consequence of a local disturbance in the cerebral circulation due to obstruction of the CBF or rupture of the wall of a vessel. Atherosclerosis is a source of brain infarcts, the initiating event for atherogenesis is injury to the endothelial lining of large to medium-sized arteries. It is clear that lipids play an important role in atherosclerotic plaque development.

Bleeding originating from fusiform aneurysm is uncommon. While the thinned arterial wall at the mycotic aneurysm may rupture early, and this event results in a clinical picture of SAH or ICH. Also the role of oncotic aneurysms in producing massive ICH is well recognized. Many vascular malformations of CNS as capillary telangiectasis, venous angioma, cavernous hemangioma and AVMs may cause significant hemorrhage to variable degrees. Ischemic stroke resulting from decreased blood flow can be the consequence of hypotensive crisis or occlusive vascular disease. Focal ischaemia due to either embolism or thrombosis may cause brain infarcts. The brain lesions attributed to ischaemia of hypotensive origin are almost always bilateral and relatively symmetrical. Two common sources of embolism to the brain are left-sided chambers of the heart and the origin of the internal carotid artery. Many brain infarcts of embolic origin are hemorrhagic because the ischemic tissue is often reperfused when the embolizing material lyses and the occluded vessel

is reopened. Embolic infarcts are relatively small in size and multiple. Thrombotic arterial brain infarct is seen in the hypertensive diabetic patient who has severe atherosclerosis of the basilar artery. The ultimate fate of brain tissues made necrotic by an arterial occlusion is the reabsorption of the dead cells by macrophage leading to the formation of a fluid-filled cavity. Lacunar infarction is destructive brain lesions of ischemic origin resulting from occlusion of penetrating arteries or arterioles as consequence of hypertension and D.M. patients with intracranial sinus thrombosis may have SAH, localized area of brain softening or infarct or pulging of numerous capillaries.

ICH being a non traumatic hemorrhage within the parenchyma of the brain may be primary (Spontaneous) or secondary as a manifestation of systemic bleeding disorder as hemophilia and leukemia.

SAH may result from rupture of aneurysms or AVMs. Large collections of blood in the subarachnoid space may produce ICH. NPs are responsible for diuresis, natriuresis and hyponatremia in patients with SAH. The physician must determine the cause and severity of acute stroke. In most hospitals the first step taken with laboratory tests is to try to image the injured site by CT or MR. MR is more sensitive than CT in showing minor examples of hemorrhagic infarction. Moreover, MR scanning offers a clear advantage over CT for imaging flowing blood allowing a diagnosis with high degree of accuracy. MR has also become the tool of choice for the demonstration of cavernous angiomas. Both CT and MR can document deep

infarcts. MR is preferred over CT for the smaller infarcts deep in the brain and for those in the brain stem. Patients with a normal CT should not be excluded from aggressive therapy, because of the delayed appearance of ischemic edema. TCD is a non invasive method that can be used to identify intracranial and extracranial arterial occlusion. It provides further relevant information that in addition to angiography helped to refine the severity of a stenosis and determine stroke pathogenesis. Meanwhile, angiography remains the proferred tool for demonstrating aneurysms and vasospasm, for easily diagnosing AVM and for separating embolism from large artery thrombosis. Xenon computed tomography blood flow imaging supplemented by SPECT, when applied quickly after infarction, deficit in local flow can be evident before tissue signal changes appear on CT or MR scan. PET scanning documented the functional metabolic response of the brain to focal infarction, and it is the best method for demonstrating viable tissue in carotid occlusive disease. PET and SPECT can determine whether the brain supplied through the stenosis or by collaterals around the stenosis or occlusion suffers from inadequate flow which has been shown to be surgically reversible.

The presence of coma increases the risk of fatality by a factor of three to seven depending on the category of stroke. The clinical outcome of the disease is not only dependent on the extent of the brain lesion but also on its localization and the development of progressive organ system dysfunction. There is increased expression of

Fas/Apo-1 in the brain tissue after an ischemic lesion, resuling in increased apoptosis that lead to aggrevated tissue damage during stroke. There is release of inflammatory mediators so the anti-inflammatory therapies are neuroprotective. CRP concentration is considered a predictor of future mortality.

The function of an ICU is to provide temporary physiological support for patients with potentially reversible organ faliure. Unselected patients with stroke appear to beneift from treatment and rehabilitation in a dedicatd stroke unit. Acute cerebral ischaemia being a neurologic emergency must be managed urgently. Maintenance of an adequate airway and proper ventilation is mandatory. Early antihypertensive therapy improves outcome in subjects in whom there is coexistent cerebral edema. Glucose control is a routine in the management of these patients and blood glucose level must be maintained as close to normal as possible. Neurologic improvement has been demonstrated when the thrombolytic treatment has been initiated in the first few hours. However, thrombolytic therapy has many complications, beside hemorrhagic risk there may be reperfusion injury associated with edema, arterial reocclusion or embolism from therapeutic lysis. On attempting to reperfuse ischemic brain, colloidal volume expansion has become a popular and successful method of treating ischemic neurologic deficits. Also, early anticoagulation had been tried after

CT although of the significant complication rate, subcutaneous low-molecular weight heparin had been tried with fewer hemorrhagic complications. Mild hypothermia has been suggested as a mean of neuroprotection. Calcium antagonists may beneficially protecting the neurons during ischaemia. Similarly free radical scavengers have been shown to be protective. An important step in management of stroke is treatment of secondary medical complications as cardiovascular and pulmonary complications, attention to nutritional and metabolic status, excretory function, bed rest and immobility and management of psychiatric and neurologic complications.

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ARABIC SUMMARY

الممرات الهوائية بكفاءة، والحفاظ على عملية التنفس بكفـــاءة، كما يجب ضبط مستوى السكر فى الدم لهؤلاء المرضى إلـــــى المستوى الطبيعى وكذلك ضبط مستوى ضغط الدم.

ومن وسائل العلاج الأخرى: محاولة تذويـــب الجلطـــات الموجودة بالأوعية الدموية، وإعطاء العقاقير التى تمنع تخـــثر الدم ولكن بعد التأكد من عدم وجود نزيف بالمخ، وذلك عـــــن طريق عمل أشعة مقطعية للمخ. كما يجب عــــلاج مضاعفـــات المرض مثل: المضاعفات التى تحدث فـــى القلـــب والجـــهاز التنفسى، ومن الأهمية تقديم التغذية السليمة والراحة ومقاومـــة قرح الفراش والعناية بعملية الإخراج (التبول والتبرز)، وكذلك يجب علاج المضاعفات العصبية والنفسية عند المريض، وذلك فى وحدات الرعاية المتخصصة، ولا جـــدوى مـــن علاجـــهم بوحدات الرعاية المركزة نظرا لإرتفاع التكاليف وعدم جـــدوى وجودهم بها.

وكذلك تصور تدفق الدم بطريقة أكثر دقة. ومن الأشعة الأخرى التى تستخدم عند التشخيص: التصوير بالدوبلر، وهى طريقة غير تداخلية تشخص إنسداد الشرايين داخل وخارج الدماغ، وهى طريقة أكثر دقة من تصوير الأوعية بالصبغة لمعرفة درجة ضيق الأوعية، ولكن لا يزال تصوير الأوعية بالصبغة هى الطريقة المفضلة لتشخيص التمددات الباثولوجية للأوعية الدموية (الأنورسما)، وكذلك العيوب الخلقية للأوعية الدموية.

ويتوقف المصير الإكلينيكى لمرضى السكتة الدماغية ليس فقط على مدى الإصابة الحادثة فى المخ، ولكن أيضا على مكان هذه الإصابة وعلى مدى وجود فشل فى بعض الأعضاء الأخرى. وقد ثبت أن هناك زيادة فى عملية موت الخلايا المبرمج لخلايا المخ فى مرضى السكتة الدماغية. كما وجد زيادة فى نسبة وسائط الإلتهاب الكيميائية، لذلك فقد يظهر هؤلاء المرضى بعض الإستجابة والتحسن عند إستخدام الأدوية المضادة للإلتهاب. وتقوم وحدات الرعاية المركزة بتقديم الدعم الفسيولوجى لمرضى السكتة الدماغية الذين يعانون من فشل فى بعض وظائف الأعضاء وكذلك يستفيد هؤلاء المرضى من العلاج والتأهيل الذى يقدم لهم فى وحدات الرعاية المتخصصة.

ويجب علاج هؤلاء المرضى دون تراخ وبعناية، ومن الأشياء التى يجب مراعاتها: المحافظة على سلامة وعمل

يحدث العجز العصبى فى مرض السكتة الدماغية نتيجة إنسداد فى إندفاع فى شرايين الدماغ، أو إنفجار الأوعية الدموية الدماغية.

تسبب الأنورسما (مرض تمدد الأوعية الدموية) ترققا فى جدار الأوعية الدموية مما يساعد على أن تنفجر بسهولة وتسبب نزيفا شديدا فى الدماغ.

ومن أسباب حدوث مرض السكتة الدماغية: إعتراض تدفق الدم فى الشرايين الدماغية بجلطة دموية مصدرها القلب أحيانا أو قد تكون بسبب إنخفاض شديد فى ضغط الدم.

ويسبب إنسداد الشرايين الدماغية موت موضعى لخلايا المخ ثم إلتهامها عن طريق خلايا الدم البيضاء الآكلة (الماكروفاج). وقد يحدث نزيف الدماغ الداخلى بدون سبب واضح، وفى هذه الحالة يكون إرتفاع ضغط الدم من العوامل المهيئة لحدوثه، أو يكون النزيف نتيجة ثانوية لأمراض أخرى مثل أمراض الدم: اللوكيميا أو الهيموفيليا.

ويجب على الطبيب تحديد سبب مرض السكتة الدماغية ومدى خطورته، وذلك عن طريق إجراء الفحوصات المعملية اللازمة، والأشعة المقطعية، والأشعة بالرنين المغناطيسى. وتعتبر الأشعة بالرنين المغناطيسى أكثر حساسية من إجراء الأشعة المقطعية، حيث أنها تشخص مناطق النزيف الصغيرة،

الملخص العربى

يعتبر مرض السكتة الدماغية من أهم أسباب الوفاة وخاصة بين كبار السن، ويأتىفى أهميته بعد أمراض القلب والسرطان، وعلى الرغم من التقدم فى سبل العلاج فإن الوقاية تعتبر أهم من حيث تقليل حدوث السكتة الدماغية الموشك، ولتكون هذه المقاومة ممكنة يجب فهم العوامل المؤدية إلى مرض السكتة الدماغية.

يعتبر مرض إرتفاع ضغط الدم من أهم هذه العوامل، لذلك فإن علاجه والتحكم فيه مهم لمقاومة حدوث السكتة الدماغية. وبالإضافة إلى إرتفاع ضغط الدم، فإن هناك أمراض القلب الأخرى المؤدية إلى حدوث السكتة الدماغية، مثل جلطة عضلة القلب، وأمراض الصمام الميترالى. ومن العوامل الأخرى التى تساعد على حدوث السكتة الدماغية: إرتفاع نسبة الكوليسترول فى الدم، ومرض السكر, ووجود البروتين فى البول، وشرب الكحوليات بكثرة، وكذلك التدخين. كما أن هناك بعض الأدوية التى تزيد من فرصة حدوث السكتة الدماغية مثل: مضادات تخثر الدم، ومضادات الصفائح الدموية، وحبوب منع الحمل.